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INSUSCEPTIBILITY OF MAN TO INOCULATION WITH BLOOD FROM MEASLES PATIENTS

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(From Base Hospitals, Camp Devens, Mass., and Camp Meade, Md.)

INTRODUCTION

In congested communities the sanitarian experiences greater difficulty in the control of diseases of the respiratory tract than in the case of those infections in which the portal of entry is by way of the alimentary canal. From the standpoint of epidemiology, measles should certainly be classified with the respiratory diseases; it takes a prominent place among the most highly communicable infections, being excelled, perhaps, only by pneumonic plague. In the mobilization of recruits even the uncomplicated cases of measles may produce a high non-effective rate; in addition to this disadvantage the serious pulmonary complications of the disease render desirable the development of a protective immunization against the primary infection. Investigations for this purpose would require the inoculation of human subjects on a basis which is necessarily more or less experimental in character. Indeed, of the serious infections of man, the virus of measles like that of scarlet fever and yellow fever * can be definitely identified only by the inoculation of susceptible human individuals. During the recent military emergency, a need and an opportunity arose for the investigation of measles such as would not occur in civil life. Accordingly, Colonel Frederick F. Russell recommended to General William C. Gorgas and to General Meritte W. Ireland the study in human volunteers of the question of prophylactic inoculation against measles. In time of need the individual soldier was found ready and willing to offer his services and to accept such risk as was inherent in these inoculations. A precedent for this type of work has been firmly established; the conditions in army life seem especially favorable for the development of preventive medicine as evidenced by the progress in the control of yellow fever, of typhoid and of trench fever.

* In a recent communication Noguchi reports the discovery of the etiologic agent of yellow fever.[1]

LITERATURE

Human Inoculations.—Accurate records of the experimental production of measles in man are meager in the extreme. The easy recognition of the disease by its clinical symptoms would seem to render of interest the investigations conducted before the bacteriologic era. For example, Mayr[2] in 1852 reported the occurrence of measles after an incubation period of two weeks in two of three subjects inoculated on the nasal mucous membrane with nasal secretions of a patient. In another experiment, Mayr reports that mild but typical attacks were produced in each of six subjects by introducing into the skin the scrapings from a morbillous lesion. The incubation period is not stated; no mention is made of any precautions to avoid spontaneous infection.

Recently Herrman[3] (1915) inoculated 40 infants under five months of age on the nasal mucous membrane with nasal secretions from cases of measles. This was done, not with the

idea of producing the disease but with the expectation of establishing an immunity, taking advantage of the relatively high insusceptibility of infants to measles in the first few months of life. None of these 40 infants developed any definite symptoms. About 1 to 2 years later, 4 of these children came in intimate contact with measles cases and two were reinoculated without developing the disease.

The first experimental inoculations of blood were performed by Hektoen[4] in 1905; this observer conducted two independent tests and reported an attack of measles in each instance. Blood for inoculation was taken during the eruptive stage and was incubated before injection, for one day at 37° C. in ascitic broth (1 part ascitic fluid to 2 parts meat infusion broth). In one patient the specimen of blood was withdrawn 6 hours and in the other 30 hours after the eruption had appeared. Moderate quantities (3 c. c. and 2.5 c. c.) were inoculated into flasks of ascitic broth (50 and 75 c. c. amounts). After incubation for 24 hours, this mixture was apparently sterile; there was no evidence of secondary contamination or of any multiplication of the virus of measles as indicated by the gross appearance, by microscopical examination and by the subsequent results of sub-inoculation on a variety of media. Accordingly subcutaneous injections were made (4 and 5 c. c.) into two volunteers and apparently a mild but typical attack of measles developed in each case after an incubation period of about two weeks. This volume of broth culture represents a calculated quantity of blood serum of approximately 0.1 c. c. All viruses known to multiply in culture media produce either macroscopic or microscopic evidence of their growth; both manifestations appear in the vast majority of cases. It would seem from these results, therefore, that a very small amount of measles blood is infective and that it retains its virulence for at least a day *in vitro* at incubator temperature. Such a conclusion is of far-reaching importance. In the investigation of a disease of unknown etiology a great advantage is achieved by the isolation of its virus in a relatively concentrated form uncontaminated by other micro-organisms; one is then in possession of suitable material for the investigation of fundamental features such as immunization of the natural host, transmission to other species and studies in morphology and cultivation. Practically the entire superstructure of modern experimental work in measles rests on these two experimental cases. One may call attention more especially to the reported transmission of the disease to monkeys by inoculations of blood and the isolation of a micrococcus from the blood stream by Tunnicliff.[5]

Inoculation of Monkeys.—Of the recent investigators, Anderson and Goldberger[6] were the first to report the successful inoculation of monkeys with measles. Two of their conclusions are of especial interest in connection with the data reported in this paper, namely: (1) that the blood of early cases is infective and (2) that the virus of the disease as it occurs in the blood is capable of passing a Berkefeld filter.

DESCRIPTION OF EXPERIMENTAL WORK

In arranging the preliminary protocol of the following work, the reported transmission of measles by the inoculation of blood was accepted as a basis for the first series of injections, arrangements being made to conduct a control for confirming the findings concerning the infectivity of the blood. In order to provide a secure foundation for the more elaborate and time-consuming experiments it was expected in the course of these investigations to obtain information concerning the constancy with which the blood of individual cases is infective, the minimal quantity which suffices to produce the disease and also the extreme limits during which the virus may be demonstrated in the blood. Inasmuch as a very favorable control for the first series of inoculations failed, the question of the infectivity of the blood in measles was accepted as the primary problem; the ultimate object of these investigations consists in determining whether a method of active immunization can be developed, without producing a serious reaction. Injections of blood from patients in various stages of the disease have been made into supposedly susceptible individuals but no symptoms of measles appeared in any instance. Two individuals who had been injected with blood were subsequently inoculated on the mucous membrane of the upper respiratory tract with nasal secretions of an early case of measles but no symptoms developed. There is some reason to believe that these individuals were protected by the preliminary injection of blood.

Arrangements and Preparations for Inoculations.—These investigations were conducted at Camp Devens, Mass., and at Camp Meade, Md. Camp Devens covers an area of approximately 16½ square miles with a normal capacity for 35,000 to 45,000 troops. The Base Hospital is situated at the extreme end of the cantonment opposite the principal entrance to the reservation. The wards of the hospital itself together with the essential accessory buildings such as the quarters and barracks for officers, nurses, and enlisted personnel, as well as the drill and recreation field, occupy an area of approximately 2½ square miles; this section is separated from the nearest barracks for troops of the line by a distance of about ½ mile. The normal capacity of the hospital is 2000 patients which in a time of emergency has been trebled. At the time of these investigations approximately 1000 troops of the enlisted personnel were assigned to the base hospital. Volunteers were obtained largely from this group of enlisted men since the majority of the medical officers had already been exposed to measles; a considerable proportion of these men had not come in contact with patients, being assigned to duty in the barracks and quarters, in the offices and on fatigue work out of doors. Conditions at Camp Meade were fundamentally identical with those at Camp Devens. The work was transferred to Camp Meade, partly for the purpose of obtaining volunteers from the more isolated rural communities, the majority of the volunteers at Camp Devens having come from the smaller towns.

Precautions Concerning Volunteers.—In the acceptance of volunteers for inoculation with measles there are two cardinal

factors which outweigh all other considerations, namely: (1) the general health of the individual with special consideration of the respiratory tract and (2) the assurance that the adult in question has never had a recognizable attack of measles.

Under ordinary circumstances the virus of measles *per se* does not produce serious results in normal individuals; its disastrous effects arise from the secondary infections. The most important of these are the pneumonias especially those from the pneumococcus, the tubercle bacillus and the hæmolytic streptococcus as in the winter of 1917-18. In addition to thorough physical examination, special attention was given to the points indicated in the following outline in order to secure the fullest possible protection for the volunteers:

I. Bacteriological cultures of throats (several examinations at intervals of three to four days) for,
   1. Hæmolytic streptococcus.
   2. Pneumococcus (any type).
   3. Meningococcus.
   4. Diphtheria bacilli.
   5. Pfeiffer bacillus.

II. Precautions against tuberculosis,
   1. History.
   2. Physical examination.
   3. X-ray findings.

III. Anatomical examination of,
   1. Tonsils.
   2. Sinuses.
   3. Middle ear.

IV. Special isolation for acceptable individuals in order to protect them from intercurrent infections and from spontaneous infection with measles.

V. Special nursing by persons of long experience with measles for any individuals contracting the disease.

If a prospective volunteer showed any of the preceding organisms in the cultural examination of the throat and nasopharynx he was at once eliminated from consideration regardless of whether the organism in question subsequently disappeared. A comparatively large proportion of individuals proved to be unsuitable either on account of the presence of the hæmolytic streptococcus or the pneumococcus. Only a few were rejected on account of a suspected latent tuberculosis. The anatomical examination of the tonsils seemed distinctly important. Individuals who had had an infection of the tonsils at all recently were not considered because, especially under these circumstances, cultural examination of the surface of the gland gives little information concerning the flora contained within the tonsillar crypts. In view of the difficulty of rigidly excluding the presence of the hæmolytic streptococcus by bacteriologic examinations it seemed much safer to conduct these inoculations at a time when infections with this micro-organism were not prevalent in camp. As a practical test of the significance of cultural examinations, Levy and Alexander[1] have noted a very low incidence of complications due to the hæmolytic streptococcus in measles cases whose throat cultures were negative for this organism.

Proper isolation possesses a two-fold importance. In the first place it was very necessary that volunteers found free of pathogenic micro-organisms should be protected from accidental contamination, especially by carriers; secondly, it is of course essential to provide against the possibility of spontaneous infection with measles. With these objects in view, the acceptable volunteers were segregated in a ward removed as far as circumstances would permit from the wards reserved for cases of measles, a distance of about ½ mile. Satisfactory isolation over the rather long period of these experiments was rendered comparatively simple by the discipline developed in military life and by the faithful cooperation of the volunteers themselves. The attendants on the ward for the volunteers were restricted from seeing any patients, but they were not required to isolate themselves. By observing the precautions just outlined, it was felt that the possible dangers inherent in these inoculations would be reduced to a minimum.

Probably the greatest difficulty in these investigations consists in the selection of susceptible adults; in the large cities only a very small proportion of individuals, perhaps 5 per cent, come to adult life without having contracted measles. Age *per se* confers no immunity. Moreover, the disease runs a clinical course which is remarkably true to form. Unrecognized attacks such as abortive cases without a rash constitute, if they occur at all, virtually a negligible factor. The chief difficulty arises from the fact that little or no dependence can be placed on the statement of even the educated adult that he has never had measles. Information was obtained according to the following plan: A census of the detachment was taken and those individuals were at once eliminated who reported having had either measles, "German measles," or scarlet fever.† These three diseases were included on account of possible errors in diagnosis. A limited number were sure that they had had none of these infections; the parents of these men were consulted. At Camp Devens this was done, whenever possible, by the individual himself in person; at Camp Meade a letter was sent to the family of the soldier. Inquiry was made in the first place concerning the individual himself, and secondly, whether he had been exposed to measles through its occurrence in other members of the family. After this information was obtained, an opportunity to volunteer was given to the men in whose cases the replies from the parents were satisfactory, provided that the preliminary bacteriologic examination of the individual was negative. The first cultures were made while the history was being obtained; the final examinations were completed only after the individual had volunteered and had been isolated.

The general plan of the inoculations was designed with the purpose of eliciting the desired information concerning the virus of measles with the production, however, of only an absolutely minimal number of cases of the disease. By employing large series of volunteers, the experimental data could have been obtained rapidly on an extensive scale but only at the cost of

† A detailed report of this census will appear in *The Military Surgeon.*

increased risk to the individuals. With the passing of the military emergency, less attention was given to the time consumed in these experiments, the primary object being to avoid the possible production of measles in man without obtaining results proportionate to the serious responsibility of human experimentation.

PRELIMINARY INOCULATIONS OF HUMAN SUBJECTS

Selection of Measles Cases.—There are two essential criteria which must be met in the selection of measles cases for subinoculation of normal individuals: (1) the patient must be secured in relatively early stages of the disease and (2) he must be free from all other infections, notably syphilis. At the beginning of this work, the collection of blood specimens was purposely delayed until after the rash had appeared; although the blood might, very possibly, be more infective in the pre-eruptive stage, it seemed advisable to duplicate conditions which had previously given positive results in human experimentation.

For the exclusion of syphilis, dependence was placed on a thorough history in all its aspects, clinical examination and the Wassermann test.

Preliminary Inoculations.—The first inoculations were designed to give preliminary information on the following points:

(1) Whether the serum alone, free from red cells, contains the virus of measles.

(2) Whether the organism of measles will pass through a Berkefeld filter.

(3) Whether a series of injections of patient's and convalescent's serum would immunize a human subject without producing an attack of the disease.

(4) Whether a previous attack of measles confers complete immunity or whether a modified attack might result in a partially immune subject with possible attenuation of the virus.

For these inoculations, blood was taken from a moderately severe case of measles 12 hours after the first appearance of the rash. At this time the Koplik spots had already disappeared, the eruption was profuse over the face, back and chest, less intense over the abdomen and only a few scattered spots had appeared on the thighs.

Immediately after collection, one portion of the blood was defibrinated and another was centrifuged for the collection of serum. Part of this serum was mixed with an equal volume of fresh serum obtained from a typical case of measles 10 days after the temperature had returned to normal. Another portion of the original serum was diluted with nine parts of physiological saline; one portion of the diluted serum was kept at room temperature for a control and the remainder was heavily inoculated with *B. prodigiosus* and passed through a Berkefeld filter (so-called N).‡

This was an old filter, much worn, which on several previous tests had successfully held back *B. prodigiosus*. When immersed in water, an additional pressure of 50 mm. of mercury was sufficient to force a fine stream of air through this filter. The time employed in filtering 25 c. c. of the diluted serum was 30 minutes and the pressure was 40 to 50 mm. of mercury; the room temperature was 22° C. Twelve cubic centimeters of the filtrate were inoculated in varying amounts on agar plates and into flasks of broth; the culture media subsequently showed no evidence of growth.

The following subcutaneous injections were made into susceptible individuals: For convenience the susceptible men will be designated by a Roman numeral and the immunes by a letter. One volunteer (I) received 5 c. c. of diluted serum (1-10) unfiltered and kept at room temperature one hour; another (II) received 10 c. c. of filtered serum (1-10 dilution) one hour after collection of the blood; a third (III) received 0.5 c. c. of a mixture of equal parts of patient's and convalescent's sera (undiluted) after incubation for one hour at 37° C.

An immune (A) who had measles 28 years previously received 7 c. c. of defibrinated patient's blood 1½ hours after collection.

None of these four individuals developed any symptoms of measles. Neither did any local changes appear at the site of injection except in the individual who received 7 c. c. of defibrinated blood; in this subject a day after the injection, moderate tenderness on pressure developed accompanied by slight erythema over the injected area. These symptoms persisted for three days.

The chief interest in these negative results centers in the control individual who was expected to contract measles. The delay of one hour before injecting this serum and also the absence of red cells might be regarded as factors contributing toward the negative result. It would appear from previous work that the blood retains its infectivity *in vitro* for at least a day. As regards the red cells, as far as we know, all diseases caused by parasites of the red corpuscles are transmitted by insects whereas droplet infection constitutes the accepted mode of transmission in measles.

The failure of filtered measles serum to infect an apparently susceptible human subject must be borne in mind in connection with the positive result reported by Goldberger and Anderson[4] upon the inoculation of monkeys with filtered serum. These investigators conducted four experiments; in the first two, the results were negative; in the third, one of four monkeys presented slight symptoms only; in the fourth experiment one of two monkeys developed an eruption 21 days after inoculation. These authors conclude that the virus of measles is capable of passing through a Berkefeld candle. No details are given concerning the size of the filter employed or the manner in which the filtration was controlled and conducted.

For the mixture of measles serum and convalescent patient's serum, it was originally intended to conduct a long series of injections gradually eliminating the convalescent patient's serum. It was also intended to hyper-immunize by several intravenous injections of measles serum the immune (A) who failed to develop symptoms after receiving a large quantity of blood subcutaneously. After an interval of one month, a second injection was given consisting of 1 c. c. of serum intravenously. This was collected from a patient 15 hours after the appearance of the rash. No symptoms of any kind resulted from this intravenous inoculation. This work was then sus-

‡ The gradations of Berkefeld filters into coarse, medium and fine (V-N-W) was found frequently to bear little relation to their actual porosity.

pended pending confirmation of the existence of the virus of measles in the circulating blood.

INOCULATION OF SUSCEPTIBLE INDIVIDUALS WITH MEASLES BLOOD

Inoculation of Defibrinated Blood and of Blood Incubated in Ascitic Broth.—The remainder of the work with susceptible individuals has been restricted to an attempt to transmit measles by the injection of patient's blood. Defibrinated blood was injected subcutaneously into two men. Cultures of patient's blood in ascitic broth were inoculated in two other men. This duplication of a method for which successful results have been reported seemed essential in view of the negative result following the inoculation of serum without preliminary incubation. None of these four subjects developed measles; neither did any symptoms appear that could be definitely attributed to the injections. The details are as follows:

Defibrinated blood from an early case of measles, 12 hours after the appearance of the rash, was injected subcutaneously in 2 c. c. quantities in the interscapular area, after a delay of 15 minutes, into two susceptible volunteers. The patient's blood (4 c. c.) without defibrination was added to ascitic broth (50 c. c.) consisting of two parts of meat infusion and 1 part of ascitic fluid. The broth was prepared without the addition of sugar and its reaction to phenolphthalein was equivalent to 1 per cent of normal acid. The ascitic fluid was yellow in color, sp. gr. 1.018 and was free from bile pigments. Repeated aërobic and anaërobic cultures showed no evidence of growth; the ascitic fluid was therefore used without preliminary sterilization. In the culture medium prepared by Hektoen the ascitic fluid was heated at 55° C. for 54 minutes. Differences of an altogether minor nature probably occurred also in the reaction and composition of the broth and ascitic fluid which was employed.

This medium inoculated with the patient's blood showed no evidence of growth after 24 hours' incubation; accordingly, two susceptible men (VI and VII) were inoculated subcutaneously in the interscapular area with 10 c. c. of this mixture of blood in ascitic broth, the mixture being shaken to include corpuscles as well as serum. This quantity represents about 0.2 c. c. of patient's serum.

During the incubation period these men were observed with special reference to:

1. Development of symptoms in the upper respiratory tract.
2. Occurrence of Koplik spots.
3. Body temperature.
4. Total and differential leucocyte count.

A record of the temperature by mouth and of the pulse and respiration was taken as a routine at four-hourly intervals during the day. The entire surface of the body was examined for cutaneous rashes, since, after inoculation, the initial lesions might appear first not necessarily on the face or chest, but on any part of the body. All of these individuals remained essentially free from symptoms.

Inoculation with Skin Lesions.—After an interval of 35 days one of the men injected with defibrinated blood (IV) and another (VII) injected with blood incubated in broth were re-inoculated by smearing the mucous membranes of the eyes, nose and throat with freshly excised morbillous skin lesions. These inoculations possessed a two-fold interest in that a positive result would demonstrate that the virus of the disease is present in the skin lesions and that these individuals who were refractory to an injection of blood were nevertheless susceptible to the disease. No definite symptoms developed. In view of these negative results, the question arose of testing experimentally the susceptibility of these men by inoculating the upper respiratory tract with secretions from the mucous membranes of active cases. The injections of blood, however, had been made from only one case of measles, a single specimen of blood having been taken. Therefore, if the use of nasal secretions should produce measles in one of these subjects, it would only establish that, in a single case of measles, one specimen of blood at a given stage of the disease did not prove infective for a susceptible host. It seemed desirable to defer tests of susceptibility until individuals could be inoculated with blood from several stages of the disease and preferably from more than one patient.

Inoculation of Blood from Pre-Eruptive and Eruptive Stages.—Accordingly for the next step, two susceptibles were inoculated on two successive days with blood taken before and after the appearance of the eruption. Control inoculations were made simultaneously into two immunes. Blood for these injections was secured from two patients; specimens were obtained from one case 30 hours and again six hours before the appearance of the rash and from the other six hours before and 18 hours after the rash appeared. None of these four subjects developed any symptoms of measles.

Of the two susceptibles selected for these injections, one (IX) gave unusually good evidence that he had never contracted measles. This individual had grown up on a farm in West Virginia and had always lived at home. He was 26 years of age being the sixth of 8 children of whom the youngest was 20 years and the eldest 38 years of age. Information was received from the mother and the eldest sister to the effect that measles had never occurred in the household. Then in adult life several older and younger brothers and sisters left home and contracted measles. Of the five older members of the family, the eldest sister contracted measles in 1910; two brothers, the second and third members of the family, developed measles in March, 1917; the fourth member, a brother, has not had measles; a sister, who was the fifth child, developed measles in 1908. Of the two younger children one, a sister, 20 years of age, has never had measles; the other, a brother, 24 years of age, did not develop measles until he enlisted in the army, having contracted the disease at Camp Shelby, Miss., in December, 1917.

On enlisting this volunteer (IX) was assigned to the medical detachment, working exclusively in the officers' quarters. He entered the hospital only on a single occasion, to visit a friend ill with tonsillitis.

In view of the prevalence of measles in the cantonments it might seem that no susceptible individual could escape infection for any length of time. However, there has been a slight but constant incidence of measles at the ports of debarkation even among the troops returning from overseas, notwithstanding the fact that measles has been widely distributed throughout the training camps of this country.

The two immunes were injected in order to test the protection afforded by an attack of measles and also to control

any minor symptoms that might appear in the susceptibles, such as slight changes in the body temperature and in the leucocyte picture. One of these immunes (A) had already been inoculated with blood on two occasions and with secretions from the mucous membranes of patients; the results were negative. The other immune (B) probably had had measles more than 30 years ago and had not previously received any injections in the course of these experiments.

For these inoculations of blood, very favorable cases of measles were obtained during a small epidemic which developed in a country district outside of the camp. Two adult patients were selected. Blood from each of these cases was mixed with 2 per cent sodium citrate in physiological saline; the two specimens of citrated blood were pooled and the mixture was injected into each subject; 24 hours later a second specimen of blood was collected in the same way from each patient and the injections were repeated. Each subject received injections of blood from two patients at two periods of the disease, *i. e.*, the equivalent of four injections in all. On the first day 10 c. c. of blood were taken from each patient, and mixed with an equal volume of citrate solution. On examination, the first patient showed numerous Koplik spots at this time and six hours later the rash appeared. The temperature was 102.8°. The second patient showed only a few isolated Koplik spots and the rash appeared 30 hours later. The temperature was 99°. These two specimens of citrated blood were mixed; each of the two susceptibles (VIII and IX) and the two immunes (A and B) were then injected with 6 c. c. of the resulting mixture, the injection being given in part subcutaneously and in part intramuscularly in the gluteal region. The maximum period of time elapsing between the withdrawal and the injection of the blood was 45 minutes for the first and 15 minutes for the second patient. A duplicate of these injections was made on the next day, 10 c. c. of blood being taken from each case and mixed with 7 c. c. of 2 per cent citrate solution. At this time the Koplik spots had disappeared in the more advanced case; the rash, which had appeared 18 hours previously, was almost confluent over the face, well developed over the chest and very sparse over the abdomen. In the second patient, the Koplik spots were abundant at this time and the rash appeared six hours later. The temperature was 102.2°. After these specimens of citrated blood had been mixed, the same men (VIII, IX, A and B) were injected with 6 c. c. quantities in the same manner in the gluteal region on the opposite side; the time elapsing between the withdrawal and the injection of the blood for the first case, *i. e.*, the one in which the rash had developed, was 40 minutes and for the second case, 10 minutes. These injections were made subcutaneously and intramuscularly in order to duplicate in the first place the manner of inoculation for which successful results had already been reported. It seemed entirely possible that a virus might find better protection for itself in the subcutaneous tissues than when exposed to the fluids and cells of the blood stream. An intravenous injection in addition to those into the tissues was not made in order to determine whether a rash, if one developed, would appear first at the site of inoculation or on the face as in the spontaneous disease. To facilitate these observations the site of inoculation was changed from the interscapular to the gluteal region.

Some slight local reactions followed these injections. At the site of inoculation one of the two susceptibles (VIII) developed well-marked induration appearing eight days after the first injection, persisting very definitely for four days and gradually disappearing during the next 48 hours. In this individual the induration was bi-lateral; in the other (IX) slight induration without any well-defined margin developed at the site of the second injection. This also appeared 8 days after the first injection but persisted for only 48 hours. In one of these men (VIII) a very transient erythema appeared for a few hours over the area of induration, on one side only, on the 10th and again on the 11th day after injection. Neither of the two immunes developed any local induration. One of these immunes (A) on being inoculated in a similar manner 5½ months previously developed a local induration entirely analogous to these two susceptibles. The local reaction, therefore, to the first injection of measles blood varied slightly in the two immunes.

SUSCEPTIBILITY TESTS

When it became apparent that no symptoms of measles would develop from these injections of blood, arrangements were made to test the susceptibility of these men by inoculating the mucous membranes of the eyes, nose and throat with the secretions from the mucous membranes of an early case of measles.

A favorable patient was found for these inoculations. A child, five years of age, the daughter of a physician was exposed to measles by the occurrence of an attack in an older sister. During the incubation period in this child, examinations were made of the nose and throat for pathogenic microorganisms, especially the pneumococcus and the hæmolytic streptococcus. None were found and as far as secondary invaders were concerned, the secretions were regarded as satisfactory. Twelve days after exposure the patient developed a moderate conjunctivitis and coryza accompanied by a temperature of 100°. During the next two days, the temperature was practically normal but on the following morning, 15 days after exposure, it rose to 102.5° with a marked increase in the conjunctival and respiratory symptoms. A few Koplik spots were present. On the following morning these symptoms persisted and profuse eruption appeared over the face spreading gradually downward over the body in the course of the next 48 hours.

Inoculations with secretions from the mucous membranes were carried out on the two susceptibles (VIII and IX), on one of the immunes (A) and on another immune (C) who had not previously received any injections. The latter, a man, 23 years of age, had had measles nine years before. Twenty days after the last injection of blood, these four individuals (VIII, IX, A and C) were inoculated on the mucous membranes of the eyes and nose with the lachrymal secretions and also on the nose and throat with the nasal secretions of the patient. This inoculation was performed on the day of the preeruptive rise in temperature in the child, *i. e.*, 12 days after exposure and four days before the eruption. A similar inoculation was made on the day before the eruption, *i. e.*, on the 15th day after exposure. On this occasion, in addition to duplicating the previous inoculations, the buccal secretions were thoroughly rubbed over the mucous membranes of the mouth and throat of the four subjects. On both days all of these inoculations were made with a sterile cotton swab slightly moistened with physiological saline. This was rubbed rather firmly over the mucous membrane of the patient and then immediately over the mucous membrane of the subject, a fresh swab being used for each inoculation. On both occasions the

four subjects were in the same room with the patient; on the day of the first inoculations, the patient not being confined to the bed was allowed to play with these men three-quarters of an hour.

Intravenous Injection of Blood.—In addition to these inoculations with secretions of the mucous membranes, one more susceptible (X) was inoculated with measles blood. A specimen was taken from this same child within from 6 to 10 hours after the appearance of the rash; 0.5 c. c. was injected subcutaneously and 1.5 c. c. intravenously immediately after withdrawal before the blood had time to clot.

Neither the intravenous injection of blood nor the inoculations of the secretion produced, in these five subjects, any respiratory symptoms or any rash. Only insignificant fluctuations occurred in the temperature and in the total and differential leucocyte count.

For the susceptibility tests in these men it might naturally be expected that control inoculations would have been conducted with a susceptible individual who had not had any previous inoculations of blood. The production of measles in a control case would furnish some additional evidence but certainly would not in any sense afford proof that these men were susceptible and had been immunized by the injections of measles blood.

In drawing conclusions concerning these inoculations of blood and mucous secretions in these susceptible men, there are two unknown factors to be determined, namely:

(1) Whether the individuals in question (VIII and IX) at the conclusion of the inoculations were immune and if so

(2) Whether the immunity was conferred by the injection of blood or acquired possibly through a previous attack of measles.

The results of the susceptibility tests leave little doubt but that these men were immune; they were exposed to natural infection by an early case of measles and they were also thoroughly inoculated artificially. The high degree of communicability characteristic of the disease leaves little room to suppose that these men might be infected by exposure now to a second case. The evidence of susceptibility of one of these volunteers (IX) is certainly much more concrete than the general arguments that can be brought in favor of a previous attack of measles. It would seem distinctly possible that the injection of blood had produced an active immunity.

A priori one would not expect that substantial immunity could be obtained without the production of marked local or general symptoms. However, in the case of varicella, Hess and Unger[5] report active immunization by the intravenous injection of the contents of vesicles without the production of subjective symptoms. It is noteworthy, however, that control individuals inoculated on the mucous membranes failed to develop varicella. Recent work by Richardson and Connor,[6] though affording no final proof, suggests the possibility of obtaining active immunity against measles without the production of definite symptoms.

Lastly it should be emphasized that conclusive demonstration of the non-infectivity of measles blood upon injection into a susceptible individual would still fail to prove the absence of the virus of the disease in the circulating blood. It is very doubtful, for example, whether a susceptible human being would be infected by the injection of a moderate amount of blood of a typhoid patient taken during the stage of bacteriæmia. It is a theoretical possibility that the blood of a measles patient might reproduce the disease when inoculated on the mucous membranes though not upon injection into the body tissues.

For the sake of convenience, the inoculations reported in the preceding pages have been collected in the following table:

TABLE OF INOCULATIONS

Individual	Material	Amount	Mode of Inoculation
Susceptible I.	Blood serum, eruptive stage.	0.5 c.c.	Subcutaneous.
Susceptible II.	Blood serum, eruptive stage, filtered.	0.5 c.c.	Subcutaneous.
Susceptible III.	Blood serum, eruptive stage, incubated with convalescent's serum.	0.25 c.c.	Subcutaneous.
Immune A.	Defibrinated blood, eruptive stage.	7 c.c.	Subcutaneous.
1 month later.	Blood serum, eruptive stage.	1 c.c.	Intravenous.
2½ months after 2d injection.	Mucous secretions, eruptive stage.	.....	On mucous membranes.
2 months after 3d injection.	Citrated blood, pre-eruptive stage.	*3 c.c.	Subcutaneous and intramuscular.
1 day after 4th injection.	Citrated blood, pre-eruptive and eruptive stage.	*3 c.c.	Subcutaneous and intramuscular.
3 weeks after 4th injection.	Mucous secretions, pre-eruptive stage.	.....	On mucous membranes.
3½ weeks after 4th injection.	Mucous secretions, pre-eruptive stage.	.....	On mucous membranes.
Susceptible IV.	Defibrinated blood, eruptive stage.	2 c.c.	Subcutaneous.
5 weeks later.	Rubeolous skin lesion.	.....	On mucous membrane.
Susceptible V.	Defibrinated blood, eruptive stage.	2 c.c.	Subcutaneous.
Susceptible VI.	Blood, eruptive stage, incubated in broth.	*0.4 c.c.	Subcutaneous.
Susceptible VII.	Blood, eruptive stage, incubated in broth.	*0.4 c.c.	Subcutaneous.
5 weeks later.	Rubeolous skin lesion.	.....	On mucous membrane.
Susceptible VIII.	Citrated blood of two patients, pre-eruptive stage.	*3 c.c.	Subcutaneous and intramuscular.
1 day later.	Citrated blood of two patients, pre-eruptive and eruptive stages.	*3 c.c.	Subcutaneous and intramuscular.
3 weeks later.	Mucous secretions, pre-eruptive stage.	.....	On mucous membrane.
3½ weeks later.	Mucous secretions, pre-eruptive stage.	.....	On mucous membrane.
Susceptible IX.	Duplicate of 4 inoculations of Susceptible VIII.		
Susceptible X.	Whole blood, eruptive stage.	2 c.c.	Intravenous and subcutaneous.
Immune B.	Duplicate of the first and second injections of VIII and IX.		
Immune C.	Duplicate of the third and fourth injections of VIII and IX.		

*Calculated amount.

CONTROL INOCULATIONS

Injection of Ascitic Broth and Normal Blood.—For the intensive inoculation of susceptible individuals with measles blood it might seem only natural to have included the injection of measles blood incubated in ascitic broth in addition to the other injections. A control series of injections, however, had already shown that normal blood in ascitic broth was not altogether free from toxic action.

The same lot of broth and ascitic fluid already described for the incubation of measles blood was mixed with normal human blood

(4 c. c. to 50 c. c. of ascitic broth) and incubated for 24 hours. Quantities of 5 to 7 c. c. were injected subcutaneously into 10 individuals; six remained practically free from symptoms. Of the other four, one immediately after injection maintained a temperature of 99° to 99.5° for nine days; another, six days after injection, developed a temperature of 100.2° accompanied by a few large papules over the forehead and a moderate degree of inflammation of the pharynx; the two others, nine days after injection, developed temperatures of 100° and 101° with definite pharyngeal symptoms but unaccompanied by any rash.

In a second group of controls with the same technique but with another lot of broth and of ascitic fluid, the reactions were similar but rather less marked. Of 10 individuals, three remained entirely without symptoms. The results in the others were as follows: in two cases, 10 days after injection, the maximum temperature in one was 99.8° and in the other 100.2°; three other cases reacted much earlier, the temperature in one on the fifth day being 100° and in the other two 99.4° on the sixth day. One case presented a slight rise in temperature on several days as follows, 99.2° on the fourth and fifth days, 99.4° on the sixth day. On these days, this man also developed a fairly extensive maculopapular eruption appearing first over the chest and then over the arms. When his temperature returned to normal the rash faded leaving pigmented areas which gradually desquamated. Another subject on the third, fourth and fifth days after injection developed a well-marked erythema which was widely distributed over the chest, back, abdomen and extremities. The temperature continued normal, except on the 13th day when it rose to 99.4°. In this second group of controls the leucocytes were counted whenever a rise in temperature occurred, but no leucopœnias were observed.

These reactions, though very mild, indicate the advisability of conducting control inoculations when similar injections are performed to test for the presence of a virus; this is especially true in view of the difficulty of duplicating exactly a rather complex culture medium. Although these symptoms did not simulate measles in any way, nevertheless the interpretation of atypical temperature curves or rashes might be confusing; the detection of a pre-eruptive rise in temperature might be very difficult when complicated by the possible effects of ascitic broth.

CLINICAL EVIDENCE

Intra-uterine Infection.—Medical literature, especially the text-books, frequently contain the statement that pregnant mothers, having contracted measles, occasionally give birth to a child with a fully developed rash. These reports of intra-uterine infection do not bear complete evidence of authenticity. In many instances, satisfactory evidence is lacking for the diagnosis of measles especially in the child; in other cases, the period elapsing after birth before the rash appears is sufficiently long to permit of extra-uterine infection. Although the cases are comparatively rare, it appears, on the other hand, that a pregnant mother developing measles at term does not ordinarily infect the child *in utero*. Lastly, the development of measles in a new-born child would not harmonize with the view that infants during the first three months of life are immune from the disease. This apparent discrepancy might be explained by Herrman's [9] statement that children of susceptible mothers are not immune from measles, a view, however, which is not supported by the natural immunity of infants to some other acute infections, notably scarlet fever and diphtheria.

Characteristics of the Eruption.—The question whether the virus of measles gains access to the circulating blood requires for a completely satisfactory answer the explanation of a striking clinical symptom. *A priori* the remarkably constant appearance of the rash widely spread over the body would seem obviously to point to the distribution of the virus by the blood-stream. Unlike the rashes of other infections, of serum disease and of the food and drug intoxications, the eruption of measles always appears first on the upper part of the body, commonly on the face, from where it spreads steadily downward over the trunk and arms reaching the lower extremities on the second or third day. This phenomenon is very striking and very constant. It has been recognized as one of the distinguishing features of the eruption of measles. The average period for this progress over the body is usually stated as two or three days with extreme limits of one to five days. In a fairly definite but less striking manner the eruption fades in the order of its appearance; thus the rash often almost disappears on the face before it is fully developed on the feet. Virtually no explanation has been suggested for this characteristic progress of the skin eruption. Von Pirquet,[10] assuming that the virus is present in the blood stream, advances the view that the rash is a manifestation of allergie and that the order of appearance of the skin lesions is directly proportional to their distance from the heart and great vessels. In support of this view, figures are given in detail of the distance from the skin lesions by way of the arteries to the heart. It is very difficult to conceive of any explanation that is consistent with the mechanical features of the circulatory system. Moreover, other exanthems which certainly are distributed by the blood-stream do not progress in this manner over the body. A notable example is small-pox; the portal of entry is probably similar to that of measles, but one commonly examines the palms for the first nodules. Von Pirquet departs widely from the accepted views in considering that the rash of small-pox resembles measles in its origin and progress over the body.

Possibly the lymphatic system offers a more satisfactory basis than the circulating blood for the explanation both of the usual point of origin of the rash and its subsequent distribution. The mucous membrane of the upper respiratory tract and of the eyes may safely be regarded as the portal of entry of the virus of measles and the seat of the primary lesion. Notwithstanding some variation in individual cases as well as some minor differences of opinion, the skin lesions usually appear first on the face. It is conceivable that the virus travels by way of the lymphatics not unlike the primary infection of the nasal mucous membrane in leprosy with the subsequent involvement of the skin of the face. The gradual progress of the measles rash has certain features in common with the spread of erysipelas, an infection which travels by way of the lymphatics. The plexus of lymphatics forming a complete network over the body would furnish anatomical communications consistent with the distribution of the rash. The valves of the lymphatic system which normally direct the flow of lymph in certain definite channels would not necessarily constitute an effective barrier against the spread of an infec-

tious agent; a rapidly multiplying virus could conceivably grow against this feeble current of lymph and also grow through the delicate valves.

The preceding discussion has been based on the hypothesis that the morbillous exanthem is produced, not by an extracellular toxin but by the action of the virus of the disease itself, in a manner analogous to what occurs in small-pox and chicken-pox. A toxin could hardly distribute itself either by the blood stream or by the lymphatics in a manner that would explain the symptoms observed in measles. The virus of the disease, if it is distributed by the lymphatics, would almost inevitably be swept into the blood stream where it might readily persist temporarily even though it did not multiply. The clinical evidence, however, can only be regarded as suggestive; experimental proof must be obtained before any final decision is permissible. The ultimate explanation of the progress of the rash of measles will be of distinct interest and value.

DISCUSSION OF RESULTS

There is, unfortunately, a striking discrepancy between the negative results following these inoculations of measles blood and the successful experiments previously reported under essentially similar conditions. A careful examination of the data recorded in this paper has failed to suggest any correlation of these diametrically opposite results. Eight apparently susceptible individuals have been inoculated with blood in various ways but none developed measles. In the selection of measles patients for these inoculations, the diagnosis both of the disease itself, especially during an epidemic, and also the stage of the disease offers little difficulty. In any negative results in adults the crucial factor is the question of susceptibility. While some of these eight individuals may in reality have been immune, it seems that, at the least, several of them must have been susceptible. As already suggested, the two who received intensive inoculations of measles blood and responded negatively to susceptibility tests may have been immunized by the injections; if one is not willing to consider the possibility of immunization there still remain six other cases requiring explanation.

There are certain points of especial interest concerning the two experimental cases reported by Hektoen. The extremely small quantity of serum, approximately 0.1 c. c., employed by this author constituted one of the significant features of his experiment. A few but not many infections can be readily reproduced by the injection of minimal quantities of blood. In cattle plague as little as 1/60 c. c. of blood may prove infective;[11] Marchoux, Salimbeni and Simond[12] produced yellow fever with 0.1 c. c. of serum.

It will be recalled that these successful experiments with measles were conducted prior to our knowledge of serum sickness; however, only homologous proteins were employed and typical serum-disease can therefore be eliminated. In the control tests reported in this paper the injection of mixtures of normal blood, ascitic fluid and broth produced a slight temperature and rash in occasional instances, but in no case could the symptoms have been confused clinically with measles.

Spontaneous Infections.—Sporadic cases of measles may develop so insidiously that even with careful isolation, the possibility of spontaneous infection during experimental inoculations must be borne in mind. A typical illustration occurred at the base hospital at Camp Devens, Mass. A patient had been in the general wards of the hospital for two months; during this period it was not possible to trace any contact with a case of measles. He was then transferred to the psychopathic ward where, after thorough isolation for one month he developed a typical attack of measles. The temperature chart showed a characteristic pre-eruptive rise accompanied by conjunctivitis and coryza. The symptoms increased; Koplik spots appeared, the temperature rose again, a characteristic rash developed followed by the usual pigmentation. It was not possible to locate any third person who might have carried the infection to this patient. Such examples are, however, so rare that it is by no means plausible that both of Hektoen's cases could be explained in this manner. This is especially true in view of the fact that the experimental subjects in question underwent a period of isolation much longer than the normal incubation time of the disease before any injections were made and they were subsequently carefully protected from spontaneous exposure.

The diagnosis of these experimental cases was based essentially on the rise in temperature after a typical period of incubation and the development of a definite rash. In both patients the rash started on the face. In one case the progress of the rash over the body is described; its distribution was almost complete in about five hours. This period would be extremely short for spontaneous measles, being much more characteristic of rubella. Information concerning the lymphatic glands in these patients would have been of some value in differentiating these two diseases. Although the injections were made over the chest and over the back it is of interest to note that the rash appeared first on the face just as when the virus enters the body by way of the mucous membrane. In one of these cases a typical bran-like desquamation is described.

Respiratory symptoms were absent in one of these cases, a feature which has led Ustvedt[13] to suggest the possibility of doubt concerning the diagnosis of measles. However, it is not at all surprising that the mucous membrane of the respiratory tract should escape involvement when one considers that the portal of entry and very possibly the seat of the primary lesion was changed from the mucous membranes to the body tissues. Such absence of respiratory involvement in *measles inoculata* would constitute a hopeful point in securing active immunization without running the risk of pulmonary complications. Likewise, from the standpoint of protective inoculation, it is encouraging to note that evidence of malaise was absent altogether in one patient and very mild in the other.

It is noteworthy that the charts in neither case exhibit any pre-eruptive rise in temperature, a characteristic which though very common is not constant in spontaneous infections and it is certainly not an essential criterion for the diagnosis of

measles inoculata. It is desirable that certain deficiencies concerning these cases should be supplied, more especially the observations concerning the leucocyte count and the occurrence of Koplik spots. This information would be helpful in the differential diagnosis.

In some respects, therefore, these experimental cases differed from the usual course of spontaneous measles notably in the rapidity of the spread of the rash, in the absence of a pre-eruptive rise in temperature, in the absence of respiratory symptoms in one case and of malaise in the other. Such modifications, however, are of an essentially minor nature and might readily be explained as the result of the subcutaneous injection as contrasted with spontaneous infection. The occurrence of such modifications in the disease, however, would require thorough confirmation.

General Considerations.—Some of the infectious diseases of man can be readily transmitted from infected to susceptible individuals by the injection of blood; such transmission has been fully demonstrated for yellow fever,[12] malaria[14] and trench fever.[15] According to the conclusions of Hektoen this same statement would also apply to measles. To appreciate fully its importance, it must be clearly borne in mind that for trench fever, malaria and yellow fever the natural portal of entry is through the skin; in measles the primary lesion occurs in the mucous membrane. By radically altering the portal of entry or the seat of the primary lesion of a given virus remarkable changes may be produced in its effect even on a highly susceptible host; the vibrio of Asiatic cholera produces infection when ingested by way of the alimentary tract but relatively large amounts of living and virulent cultures can be injected subcutaneously with impunity.

After noting certain definite exceptions it would seem possible to develop some general rules concerning fundamental principles involved in the artificial immunization against any given infection. Precise data, from the very nature of the subject, are not available on account of the difficulty of obtaining information concerning the infectivity of pathogenic micro-organisms for man. The subject may be conveniently considered under three headings:

1. *For those infections in which the mucous membrane constitutes the portal of entry and in which the classical lesions of the disease are in general limited to the tissues accessible by direct continuity, the causative organism may in many instances be injected subcutaneously in a viable condition in moderate dosage with impunity.*

In the case of bacillary dysentery and Asiatic cholera, living attenuated cultures of the causative organism have been used freely by subcutaneous injection as a vaccine. For the pneumococcus, Cecil and Blake,§ at the Army Medical School, have recently demonstrated in monkeys (*Macacus syrictus*) that as little as one-millionth of a cubic centimeter of a broth culture may produce a fatal pneumonia upon intratracheal injection. The subcutaneous injection of one-thousandth of a cubic centimeter of the same culture may or may not produce a septicæmia. In either case, those animals which recover possess a distinct immunity. In the case of *B. diphtheriæ* virulent strains growing on a wound usually produce no symptoms in man. From the clinical evidence one would not expect that the hypothetical organisms of whooping cough and of influenza would produce an infection upon subcutaneous injection.

2. *As a corollary to the first statement, when the natural portal of entry of a pathogenic organism occurs through the skin, then artificial injection into the tissues or blood stream causes an infection which reproduces the typical manifestation of the spontaneous disease.*

Of the more important diseases in which the portal of entry occurs through the skin we may consider bubonic plague, tetanus, glanders, anthrax, malaria, trypanosomiasis, hydrophobia, kala azar, relapsing fever, typhus fever, yellow fever, dengue fever, trench fever and the spotted fever of the Rocky Mountains. In the case of plague, malaria, yellow fever, trench fever, typhus and probably dengue, it has been demonstrated experimentally that the subcutaneous or intramuscular injection of the virus, in virulent form, reproduces the typical features of the spontaneous disease; a similar result could be confidently expected in the remainder of the diseases just mentioned.

The disease, plague, occupies a position of an intermediate type which is unique. *B. pestis* exhibits the characteristic of possessing two distinct portals of entry resulting in the production of two clinical types of disease, the pneumonic and the bubonic form of plague. If insect transmission of *B. pestis* were unknown, bubonic plague would not occur spontaneously; experimentally it could be designated appropriately as *plague inoculata* inasmuch as it differs markedly from the pneumonic form.

3. *For those infections in which the virus enters by way of the mucous membrane and gives rise to metastatic lesions in other tissues of the body, the injection of the virus into the body tissues usually produces an infection; sometimes the essential clinical characteristics of the disease are duplicated, but in other instances a modified infection results quite unlike the spontaneous disease.*

The first and third groups must be looked upon merely as extremes between which there can be no sharp dividing line; for instance, typhoid fever constitutes a somewhat intermediate example. Although *B. typhosus* can infect in moderately small numbers by way of the mucous membrane, nevertheless, living cultures can be injected subcutaneously with the production of nothing more than a local reaction.

The meningococcus, *M. melitensis, Treponema pallidum* and the causative organism of poliomyelitis may conveniently be considered together. Injection of monkeys with the virus of poliomyelitis and the accidental injection of man with *T. pallidum* have produced typical infections; similar results could probably be obtained with the meningococcus and with *M. melitensis,* two organisms which produce little or no local lesion on their passage through the mucous membrane.

Small-pox and chicken-pox present important conditions for consideration. When the virus of small-pox is inoculated

§ Personal communication.

on the skin instead of on the mucous membranes, *small-pox inoculata* develops and the disease, as it occurs spontaneously, cannot be reproduced in this manner. According to Hess and Unger[9] the virus of chicken-pox, when injected intravenously, gives rise to no symptoms but apparently reproduces some immunity.

Exceptional conditions occur in two of the diseases of lower animals. In cattle plague extensive primary lesions occur on the mucous membrane of the intestinal tract and eventually a septicæmia develops. Experimentally the virus behaves in an almost unique manner in that small doses of blood injected subcutaneously set up a fatal infection. Besson[10] states that the influence of the site of injection of the bacillus of symptomatic anthrax is very marked. A dose of the virus which will kill an ox on injection into the cellular tissues of the body will produce merely a benign infection when injected into the connective tissues of the neck, tail or ear and is followed by permanent immunity.

In the preceding discussion the objection may at once be raised that the normal healthy adult can readily withstand the inoculation of a few living and fully virulent pathogenic organisms. A distinct step would be gained if it can be shown that those organisms which normally enter the body through the skin can, as far as injections into the tissues are concerned, set up an infection from the introduction of much smaller numbers than in the case of those micro-organisms which first infect the mucous membranes. In attempting prophylactic immunization against a given disease it is fundamentally necessary to consider the natural portal of entry of the virus in question.

RESUME

An effort has been made to determine whether the virus of measles exists in the circulating blood of a patient, permitting the transfer of the disease from man to man by the inoculation of blood. The prominent data bearing directly on this subject are:

(1) The successful transmission in two cases previously reported by Hektoen,

(2) The failure in eight instances recorded in this paper to transmit measles by the injection of blood,

(3) The clinical phenomenon of the origin of the rash on the face or upper part of the body with its gradual progress downward requiring from one to three days to complete this march.

The symptoms of the two experimental cases that have been reported were not entirely characteristic of the classical type of measles. Although the disease varies extremely little in its clinical manifestations, distinct modifications might readily occur under experimental conditions.

As regards the negative results obtained in these eight individuals, the principle difficulty arises in establishing, by the clinical history, the susceptibility of an adult to a disease so generally prevalent as measles. In some of the men who were inoculated the circumstantial evidence of susceptibility was unusually strong.

Failure to transmit the disease by the injection of blood does not preclude the existence of the virus in the blood stream even in moderate amount. There is some evidence that these men not only failed to become infected but that they were actively immunized by the injection of blood; such an assumption would, of course, presuppose the existence of the virus in the blood stream. Indeed the agent which excites the rash might readily gain access at least temporarily to the blood-stream regardless of whether its distribution takes place by the lymphatics or by the circulating blood.

The constant origin of the eruption on the upper part of the body and its gradual and orderly extension downward is quite unlike the development of eruptions in which the virus is known to be distributed by the circulating blood.

Measles originates as an infection of the respiratory and conjunctival mucous membranes and the virus does not set up metastatic infections in the viscera of the body in the spontaneous disease. Failure to reproduce the disease by subcutaneous injection of the virus is in keeping with the behavior of several other pathogenic micro-organisms of the respiratory and gastro-intestinal tract.

The virus of measles *per se* does not produce serious effects, but one attack of the disease gives rise to a well-marked immunity. With appropriate isolation of the virus it would seem that a substantial active immunity should be obtainable with a minimum of inconvenience to the individual.

CONCLUSIONS

1. The question of the transfer of measles from man to man by the injection of a patient's blood is entirely reopened by the eight successive negative inoculations recorded in this paper.

2. The failure to transmit the disease in this manner does not necessarily exclude the possibility of the occurrence of the virus of the disease in the circulating blood; some evidence was obtained indicating the possibility of producing active immunity by the injection of patient's blood.

This experimental study of measles by the inoculation of volunteers was authorized by General Gorgas and General Ireland at the request of Colonel Frederick F. Russell. The officers and men volunteering for this work signed the following statement:

"I hereby volunteer as a subject for inoculation with measles in order to promote the work undertaken in the United States Army for securing a protective inoculation against this disease."

Having seen the serious consequences of measles in camp life, these men, for no reward to themselves, gladly accepted the risk inherent in these inoculations simply from a desire to be of service. Throughout this work they co-operated cheerfully and conscientiously in carrying out the long isolation essential during these investigations.

The Surgeon General's recognition of their services was made by Colonel Russell in the following letter:

"The Surgeon General has been informed of the fact that you volunteered for the measles investigation. He desires me to express to you his appreciation of the patriotism and devotion to duty that you have shown and to assure you that your contribution to the cause is appreciated by him just as much as was the bravery of the men who went into the fight in France."

It is a pleasure to acknowledge the constant co-operation of Colonel Frederick F. Russell throughout these investigations. I

am especially indebted to Lieutenant-Colonel Channing Frothingham for his assistance at Camp Devens and to Lieutenant-Colonel Henry J. Nichols for his kind co-operation at Camp Meade and at Washington, D. C.

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THE RÔLE OF THE X-RAY IN THE DIAGNOSIS OF LONG-STANDING RENAL TUBERCULOSIS

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The progress which has been made in the last decade in the investigation of diseases of the urinary tract, thanks to the use of the cystoscope and ureteral catheter, has made possible a differentiation of lesions which before that time had been unrecognizable.

There is no disease of the kidney which can be more certainly diagnosed by the use of these modern methods than renal tuberculosis. The demonstration of diminution in the renal function, together with the presence of pus cells and of tubercle bacilli in the catheterized specimen of urine collected from one side, leaves no possibility of doubt as to the condition with which one has to deal.

In the majority of cases a diagnosis is possible by the use of these methods. But in many cases of renal tuberculosis, especially those of long duration, cystoscopy and ureteral catherization are impossible on account of the changes which have taken place in the bladder mucosa. It may be impossible to recognize the ureteral orifices or they may not admit the ureteral catheter; and there are also some cases in which extensive ulcerative processes have led to such contracture of the bladder as to make the introduction of the cystoscope impossible or too painful for the patient to bear. In many of these cases, although tubercle bacilli may be demonstrable in the bladder urine, owing to the fact that the ureters cannot be catheterized, it is impossible to determine in which kidney the lesion is located, because it must be remembered that in most cases of renal tuberculosis there are a few definite symptoms referred to the kidney itself.

When it is possible to introduce the ureteral catheter, the diagnosis is usually easy, but there are types of long-standing chronic tuberculous processes with sluggish ulceration in which only a few pus cells can be demonstrated and tubercle bacilli may not be found even in repeated catheterized specimens.

In some cases in which the disease has progressed to complete destruction of the kidney terminating in caseation and deposition of calcium salts—the so-called auto-nephrectomy—the deposition of calcium salts will cast a shadow on the x-ray negative varying in density in proportion to the extent of the process. It is in just these cases where for any of the above reasons a definite diagnosis cannot be made that the x-ray will often be the determining factor in the recognition of the lesion.

When the normal kidney substance has been largely replaced by calcified caseation, a complete outline of the kidney and even the ureter may be seen on the x-ray plate and in such cases a definite diagnosis can be made immediately without the demonstration of tubercle bacilli and without recourse to ureteral catheterization except to determine the integrity of the opposite kidney.

It should, therefore, be a routine procedure to precede cystoscopy and ureteral catherization by plain x-ray examination of the urinary system in all suspected cases of renal tuberculosis.

When the calcification is limited to a single area in the kidney there may be some difficulty in differentiating this process from calculus, but a critical observation of the

density, shape and position of the shadow, will leave little room for doubt. Where the kidney has been completely destroyed, the characteristic lobular appearance of the shadows due to the calcified caseous cavities is very definite and is never seen in any other type of kidney lesion.

By means of stereoscopic plates the individual abscess cavities can be clearly distinguished from each other, provided, of course, that the process has been of a duration long enough to produce deposition of calcium salts in the areas of caseation. Calcification of the ureter is rare, but when it does appear it is perfectly characteristic, the ureter showing on the negative as a dense shadow, the calcification involving the upper portion, the lower portion or indeed its entire course.

In addition to what is shown by the sclerosis of the ureter itself, a shadow may be cast by the caseous material which is sometimes seen filling the lumen of the ureter and which represents the contents of the cavities in the kidneys.

The fact that calcification occurs as a late process in renal tuberculosis and that this calcification will show an opacity on the x-ray plate has long been known, but the practical value of this simple method has been too little emphasized.

During the past few years several cases of renal tuberculosis have been recognized at the Brady Urological Institute from the x-ray plate alone, and a summary of some of the more interesting of these cases will be given in order to emphasize the value of the routine x-ray examination.

CASE 1.—A physician, aged 39, was seen in 1907. The family and past histories were unimportant. The patient had had attacks of dull pain in the back and left flank at the age of fourteen which were diagnosed at that time as indigestion. He first noticed frequency and burning on urination at the age of twenty associated with hematuria. He lost some weight, had chills and fever and was incapacitated for about one year. A careful urinary examination was apparently not done at this time. The blood, however, soon disappeared and the frequency was greatly improved by instillations of silver nitrate. The dull pain in the back and left side, however, persisted, varying in intensity from time to time, and this was the patient's only complaint when he came for consultation.

The physical examination was negative and there was no tenderness in the region of the kidney nor could either kidney be felt. The urine was clear and contained no shreds or pus cells and on this account no examination for tubercle bacilli was made. There was evidence of a chronic prostatitis on rectal examination and the prostatic secretion contained an excess of pus cells.

The patient improved under prostatic massage, irrigation, instillation and dilatations of the prostatic urethra, until the pain completely disappeared. He was then referred to a gastro-intestinal consultant and in the course of an x-ray examination of the gastro-intestinal tract following the ingestion of bismuth a remarkable shadow was seen in the region of the left kidney. This shadow occupied the position of the kidney and showed a definitely lobulated appearance. Nothing similar had been seen at the Johns Hopkins Hospital at this time and a positive diagnosis was not made. Cystoscopic examination showed a normal bladder with the exception that the left ureter could not be seen. The right ureter was easily catheterized and the specimen obtained was normal. A diagnosis of ureteral stricture with destruction of the left kidney was made, but the tuberculous nature of the process was not recognized.

The patient went to a western clinic where a nephrectomy was done and the kidney substance was found to have been entirely replaced by caseation and masses of calcification.

A letter dated April, 1919, states that the patient has been "free from pain and a great deal better since the operation."

The correct diagnosis of this case should have been made from the x-ray alone, but at this time no similar shadow had been seen in the x-ray department. The entirely negative urinary examinations and the fact that the patient responded so well to local treatment were also confusing factors which contributed to the failure to recognize the true nature of the process. (Fig. 1, Case 1.)

CASE 2.—A male, aged 24, consulted Dr. Geraghty in June, 1914, complaining of frequent urination. His father and two uncles had died of pulmonary tuberculosis. The past history was unimportant.

Frequency with burning had existed for the past two years with little or no improvement, at times associated with terminal hematuria. There was also at times a dull aching pain in the back mostly on the left side. A left epididymitis had appeared two years before, followed ten months later by a right epididymitis.

On examination there were no evidences of pulmonary tuberculosis. Neither kidney could be felt. The left testicle was normal; the epididymis was thickened at the globus minor where it was adherent to a scar in the scrotum. The right testicle and epididymis were much obscured and the globus minor was firmly adherent to a scar in the lower portion of the scrotum. The vasa deferentia were normal. The urine contained some pus cells but no tubercle bacilli.

Cystoscopic examination showed a contracted bladder. The mucosa showed some areas of reddening especially in the trigone, but there was no active tuberculosis. The right ureter was seen but it was impossible to catheterize because the cystoscope could not be introduced far enough to permit a ureteral catheter to enter it. The left ureteral orifice could not be seen.

Plain x-ray examination showed a definite dense shadow occupying the region of the left kidney. This shadow suggested a lobular form, but it also presented a somewhat granular appearance. The ureter, which was not enlarged, could also be plainly seen in its entire course from the kidney over the pelvic brim to the bladder.

A diagnosis of left renal tuberculosis was made and nephrectomy was done by Dr. Geraghty. Convalescence was uneventful. The kidney was lobular, twice the normal size and had been entirely converted into a cheesy mass. The ureter was very thick and fibrous, its lumen entirely filled with caseous material and practically obliterated. (Fig. 2, Case 2.)

CASE 3.—A man, aged 24, came for a consultation in June, 1914, complaining of frequent urination. The patient's father and two uncles had died of pulmonary tuberculosis. The past history was unimportant. The patient had first had frequency, strangury and hematuria two years before and shortly after the onset a left epididymectomy was done for epididymitis. A year and a half later the left testicle was removed on account of a persistent sinus.

Since this date the frequency had persisted and there had been pains in the region of the bladder but none in either kidney region.

Physical examination revealed no signs of pulmonary tuberculosis, the left kidney was palpable but not tender. Rectal examination revealed irregular induration of the left lobe of the prostate and seminal vesicle.

Plain x-ray examination showed both kidneys definitely outlined and larger than normal. A definite, rounded mass was seen in the region of the left kidney which closely resembled

the shadow of a stone. On the right side there was a definite, lobulated irregular shadow not so dense as that on the left side but much larger, the process evidently involving the left kidney more than the right.

Cystoscopy showed a reddened trigone and some areas of cystitis but no active ulceration. The ureters were easily catheterized and the specimens from each side contained a few pus cells and a few large colon-like bacilli. The 'phthalein excretion from each side was 18 per cent. No tubercle bacilli could be found in these specimens, nor had any been demonstrated in the bladder urine after repeated examination. A guinea-pig innoculation was also negative.

A *pyelogram* showed a normal right pelvis, the calyces being somewhat elongated, the superior calyx extending as far as the shadow seen on this side. The ureter was not dilated. The left pelvis was normal but the calyces were greatly elongated and extended out so that they more or less surrounded the oval shadow previously seen on this side. The results of this examination tended to support the tentative diagnosis of calcified tuberculous areas in each kidney.

It was decided to explore the left kidney to determine definitely the nature of the shadow. At operation, Dr. Geraghty immediately confirmed the tentative diagnosis from the appearance of the kidney delivered in the wound. On account of the involvement of the right side the kidney was replaced and the wound closed. Convalescence was uneventful. (Fig. 3, Case 3.)

Case 4.—Physician, aged 41. This patient was seen by us in a base hospital in France having been referred on account of hematuria. His mother had died of pulmonary tuberculosis. His past history was negative except for a left empyema in 1903.

He had noticed blood in his urine first in 1898 and this had continued for about two years with few or no bladder symptoms. The diagnosis of prostatitis had been made and local treatment given. In 1902, blood had reappeared in his urine and continued for a short time. In 1906 for the same symptom the patient had gone to a western clinic where cystoscopy was performed but it was found impossible to catheterize the right ureter. From this time on the same slight frequency of urination had persisted. Following the exposure incident to foreign service the hematuria had reappeared in October, 1918. Physical examination was negative except for the scar of the empyema operation. Examination of the urine showed numerous pus cells and red blood cells but no tubercle bacilli.

Cystoscopic examination showed a small ulcerated area on the anterior bladder wall and rather marked injection of the trigone. The left ureter was readily catheterized but no definite right ureteral orifice could be made out in spite of repeated attempts. The urine from the left kidney was normal.

A definite diagnosis could not be made but tuberculosis of the right kidney was suspected and the patient invalided home to the States for further study.

On entrance to the Brady Urological Clinic after repeated examination of the urine a few tubercle bacilli were found, the cystoscopic findings were corroborated and the plain x-ray examination showed a clear outline of both kidneys, the right kidney being smaller and the shadow remarkably opaque. On careful observation a definite dense lobulated appearance was seen and the ureter which was distinctly opaque could be easily made out in its course to the bladder.

In the plain x-ray of the pelvis the lower end of the right ureter showed the same distinct opacity and its shadow could be seen coursing over the brim of the pelvis. The outline of the left kidney showed no opacities and the organ could be definitely seen to have undergone compensatory hypertrophy.

From the characteristic dense lobular shadows seen in the plain x-rays and the demonstration of tubercle bacilli in the urine a diagnosis of right renal tuberculosis was made and a nephrectomy was performed by Dr. Geraghty, December 13, 1919. Convalescence was uneventful.

The kidney was found to be entirely destroyed, all kidney substance having been replaced by caseated masses separated from one another by thin layers of fibrous tissue. The ureter was entirely obliterated.

This case was evidently one of very long standing, slowly progressing, the initial symptoms dating back twenty years. In spite of this long duration the bladder had become only very slightly involved and tubercle bacilli were found only on one occasion among many examinations.

It is this type of slowly progressing lesion which results most commonly in the so-called auto-nephrectomy and it is in just this class of lesions that calcium salts are deposited in amounts large enough to permit a diagnosis to be made from the plain x-ray plate positive. (Fig. 4, Case 4; Fig. 5, Case 4.)

Case 5.—A man, aged 46, entered the Brady Urological Institute in May, 1919, having been referred with a diagnosis of left renal tuberculosis. His family history was negative. At the age of nineteen an abscess of the left testicle had been opened and eighteen months later two abscesses had been opened in the right lumbar region. Six years before he came to us a severe attack of renal colic on the right side had been followed by the passage of a small calculus and four years later a similar attack occurred on the same side. There had been no frequency, hematuria or pain on urination, but the patient had had a dull aching pain in the region of the left kidney and soreness in the left hip for the past few years. The patient was seen about one year before but the left ureter could not be catheterized.

Physical examination was negative except for slight tenderness elicited on deep pressure over the left kidney. Neither kidney could be felt on account of the thick abdominal wall. The scars of the old abscesses in the right lumbar region were well healed. The urine was clear, contained no pus cells and no tubercle bacilli.

Stereoscopic x-ray plates were taken of the left kidney and the whole organ was represented by a series of lobulated shadows which without doubt represented the calcification of the individual areas of caseation. Nine such lobules could be easily counted on the stereoscopic plates. The shadow of the right kidney showed that it had undergone compensatory hypertrophy. There were also evidences of an old healed tuberculous process involving the first, second and third lumbar vertebrae. The total function as measured by an intramuscular injection of 'phthalein was normal. The patient was advised to return later for nephrectomy.

Although operation has not as yet been carried out on this patient there can be no doubt as to the diagnosis or as to the integrity of the right kidney. One may also assume that the left ureter has been occluded and that the process commonly called auto-nephrectomy has also occurred in this case. (Fig. 6, Case 5.)

A dogmatic classification of the shadows cast by various types of tuberculous kidneys cannot be made and all graduations may occur, from the small indefinite shadow cast by a calcified, tuberculous area about a calyx, to the beautiful lobulated shadow which results from a completely destroyed kidney, consisting entirely of calcified abscess cavities. The x-ray of such a kidney is quite unmistakable, but the smaller, indefinite shadows which may be seen are occasionally difficult to differentiate from renal calculi and also from various extra-renal shadows such, for example, as the contents of the intes-

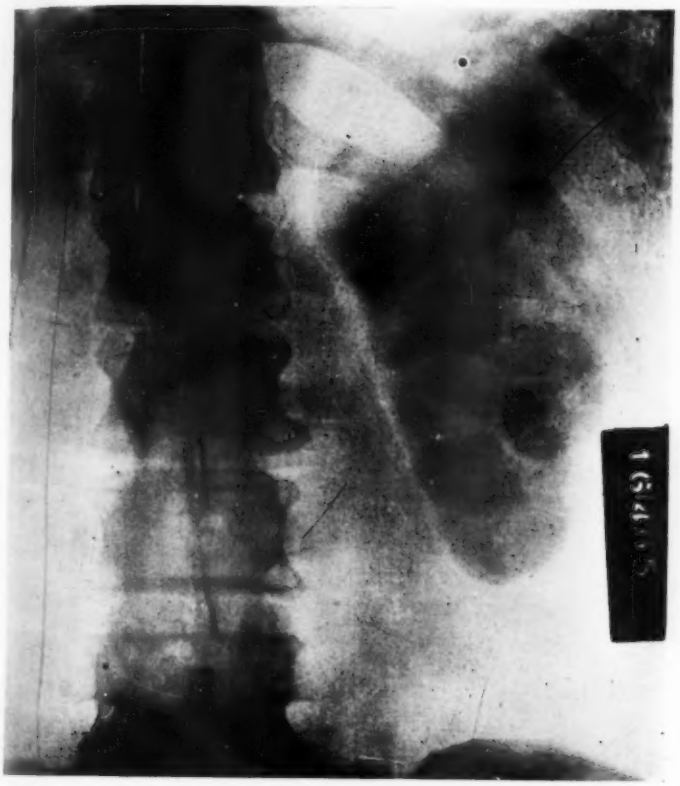

FIG. 1 (Case I).—Characteristic lobulated appearance of a kidney completely destroyed.

FIG. 3 (Case III).—Complete destruction of the upper pole with beginning deposition of calcium salts in lower pole of a kidney not yet completely destroyed.

FIG. 2 (Case II).—Typical mottled appearance due to the irregular deposition of calcium salts in a kidney completely destroyed. The outline of the ureter is plainly seen.

FIG. 4 (Case IV).—Completely occluded kidney with deposition of calcium salts throughout its entire extent.

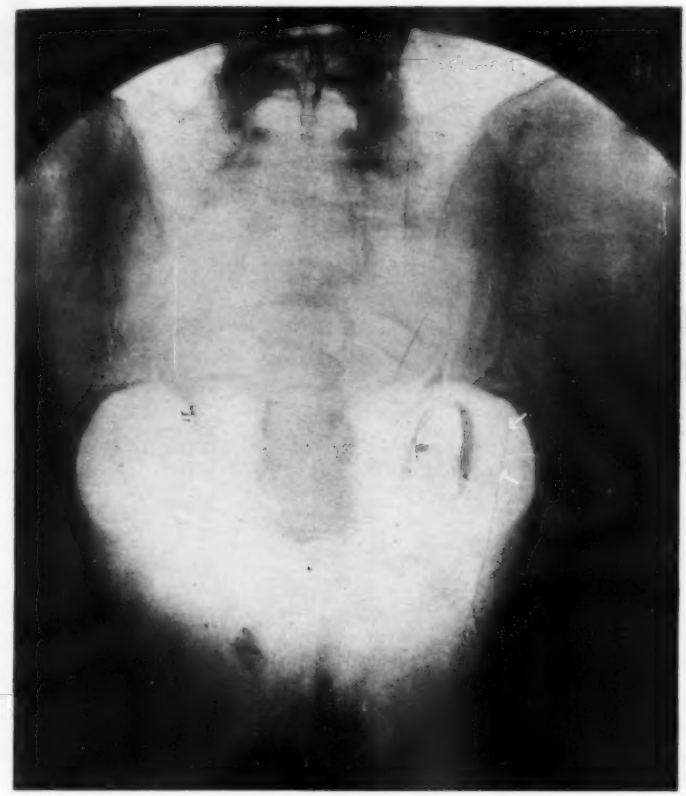

FIG. 5 (Case IV).—Calcification of the lower end of the ureter in Case IV. Same side.

FIG. 7.—Drawing of the stereoscopic plates of Case V, showing the clear differentiation of the individual calcified lobules.

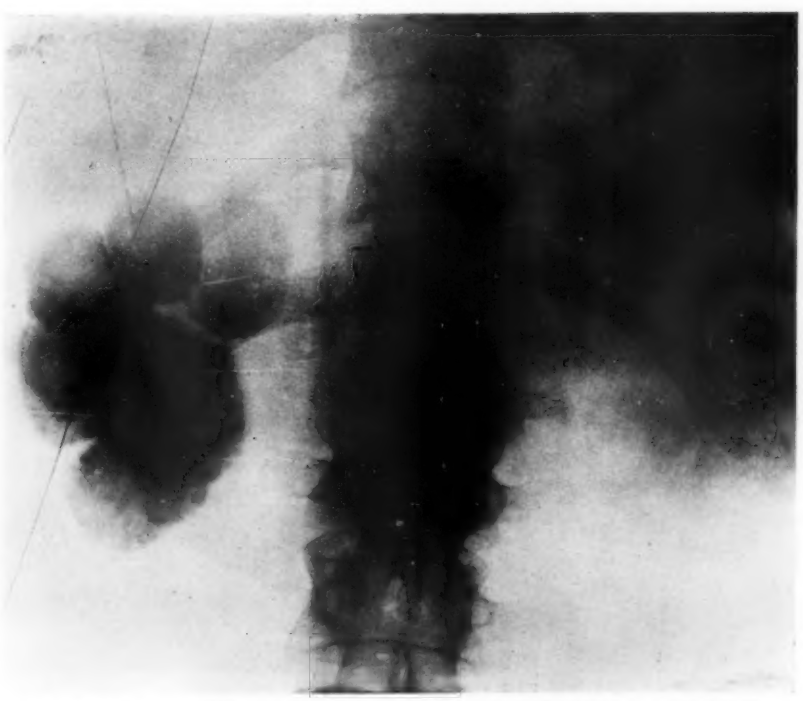

FIG. 6 (Case V).—Kidney completely destroyed, showing typical lobulated form with deposition of calcium salts in the caseated areas. Old healed tuberculous process of the twelfth thoracic and first and second lumbar vertebræ.

tine, calcified glands, gallstones, etc. It must also be remembered that the extent of the shadow on the x-ray plate does not represent the extent of involvement of the kidney and many kidneys have been seen, on removal, totally destroyed, which, on x-ray examination, showed only small indefinite shadows, or none at all.

The presence of a true renal calculus, in association with renal tuberculosis is rare, but several such cases have been seen in which a calcium oxalate stone occupied the pelvis of a tuberculous kidney. In all probability such a stone arises from the deposition of calcium salts in a tuberculous ulceration of a calyx. We have seen several cases of early tuberculosis in which the only focus found in the kidney after the operation was an ulceration of a single calyx. In a few of these cases there was a definite deposition of calcium salts and it is easily conceivable that a small portion of such a calcified area could break off, fall into the pelvis and form the nucleus of a large stone.

Such a stone gives a picture quite different from that occasionally encountered when a tuberculous area in a kidney, wrongly diagnosed as a stone, is exposed at operation. If an attempt is made to remove the supposed stone it will be found to consist of a grumous, putty-like material which cannot be taken out as a whole. If such a condition is encountered and its true nature recognized at operation, it is far better to do a nephrectomy provided previous studies have demonstrated that the remaining kidney is normal. However, if the x-ray shows the presence of similar areas in the remaining kidney or if the evidence of its involvement has been demonstrated, no operative procedure should be attempted, as the trauma incident to operation may very readily convert a slowly progressing, partially walled-off process into an acute exacerbation or may even lead to a general miliary tuberculosis.

It is not the purpose of this paper to discuss the very great assistance of the data which may be obtained from the pyelogram and cystogram. In an occasional case when sufficient information cannot be obtained by other means, a diagnosis can be made by these studies. It has been the practice at the Brady Clinic, however, to refrain from a pyelographic study if a definite diagnosis of renal tuberculosis can be made by the usual methods. There have been no bad results following this method but we have not felt that in cases where the diagnosis was already certain the additional instrumentation was justified.

CONCLUSION

(1) X-ray studies of the entire urinary tract should be carried out in all cases of suspected renal tuberculosis.

(2) In some cases, when other methods of examination have failed, a definite diagnosis of renal tuberculosis can be made from the plain x-ray alone but, whenever possible, catheterization of the other ureter should be done to establish the integrity of the opposite kidney.

(3) The shadows depend entirely upon the amount of calcification which has taken place in the diseased kidney.

(4) Various types of shadows may be seen in the plain x-ray of a tuberculous kidney varying from the indefinite shadows cast by small areas of calcification to the characteristic lobulated shadow which is typical of a completely destroyed kidney.

(5) Pyelography and cystography may clear up the situation in some cases but these procedures should not be carried out if a diagnosis can be made by other and simpler methods.

NOTE.—Since this article was written a paper by Braasch and Olson (Roentgenographic Diagnosis in Renal Tuberculosis, Surgery, Gynecology and Obstetrics, XXVIII, 6, p. 5551) has appeared in which virtually the same conclusion has been reached.

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REPRINT OF THE OSLER NUMBER OF THE BULLETIN

The demand for copies of the Osler number of the Bulletin has exceeded the number of copies printed. Should a sufficient number of requests for additional copies of this number be received by October 1st to justify another issue, it will be reprinted and sold for $1.00 per copy. All those interested in securing copies should send in their orders promptly to

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IN MEMORIAM

ADMONT HALSEY CLARK

By William G. MacCallum

A memorial meeting was held on June 9, 1919, in the lecture room of the Pathological Laboratory of The Johns Hopkins University to uncover a tablet placed there by colleagues and friends to the memory of Dr. Admont H. Clark, associate professor of pathology, who died on October 13, 1918. The admiration and affection of all who had known him were expressed in brief addresses by Dr. Welch, Dr. Howell, Dr. Sabin and Dr. MacCallum. The following short biographical sketch was read:

Admont Halsey Clark, the eldest child of Cyrus Alonzo and Harriet Gulick Clark, was born near Kyoto, Japan, on August 25, 1888. His father, who came from Genesee County, New York, had graduated as a minister at Oberlin College. His mother, whose family, the Gulicks, had for generations been missionaries, was born in the Caroline Islands.

Their married life has been almost entirely spent in missionary work in Japan and there Admont lived and went to school until he was 12 years old. After that he was sent to America to be educated and came to live with his mother's sister and her husband, who is Professor Jewett, of Oberlin College. With them he remained through his school and college life, becoming deeply attached to this aunt and uncle who in some degree took the place of his distant parents.

All through his student career, both at Oberlin and later in the medical school, he earned money by every kind of outside work to support himself. Nevertheless, he found time enough for his studies to stand well in his classes, and playtime enough to excel at athletic sports. He was a particularly good player at football and was on the University and the Maryland State teams. Music, too, he loved and during this whole time he studied the violin and learned to play it very well, so that later he derived great pleasure from taking part in trios and quartets.

After his graduation at Oberlin College in 1910 he formed one of a party of biologists on an expedition to Point Pelee on Lake Erie to observe the migratory flight of birds and to learn whether they flew boldly across great bodies of water or tried to take advantage of the islands scattered across the lake. Here he contracted typhoid fever which was so severe that he lost a whole year before entering The Johns Hopkins Medical School in 1911. During part of this time, however, he acted as assistant in chemistry at Oberlin College.

When fully recovered, he began work with a new zest. At college he had taken up scientific subjects, showing especial interest in chemistry toward which he had probably been led by Professor Jewett. Again he stood high in his class and, in addition, he proved to be one of the men who can and must work on special problems which carry them beyond the routine work of the class.

Each year he seems to have been hard at work on one or more problems, as his published papers show. In the first year he worked under Dr. Sabin's direction on the development of the lymphatics, in the second under Dr. Whipple on the chemical tests of the function of the liver. In his fourth year he substituted as interne in the hospital for two months and there devised and worked out a method for studying venous pressure in disease. He graduated with the degree of Doctor of Medicine in 1915 and entered immediately the department of pathology where each year he advanced, beginning as an assistant and becoming successively instructor, associate and associate professor of pathology.

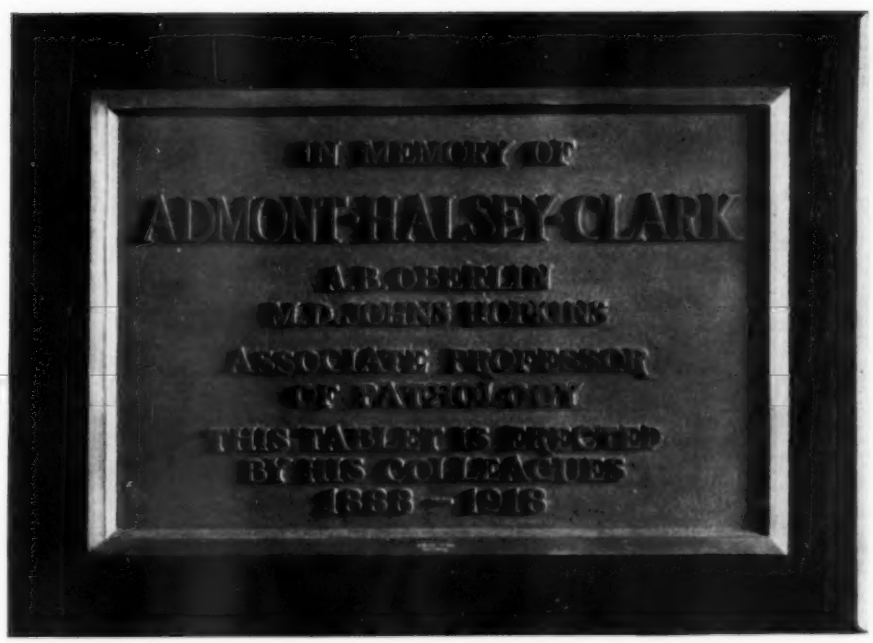
In these positions he showed his ability to carry out serious investigations independently and proceeded to a long and most laborious study of the internal secretion of the pancreas in its relation to sugar metabolism. This was brilliantly successful in demonstrating the presence of a secretion essential to the consumption of sugar by the beating heart.

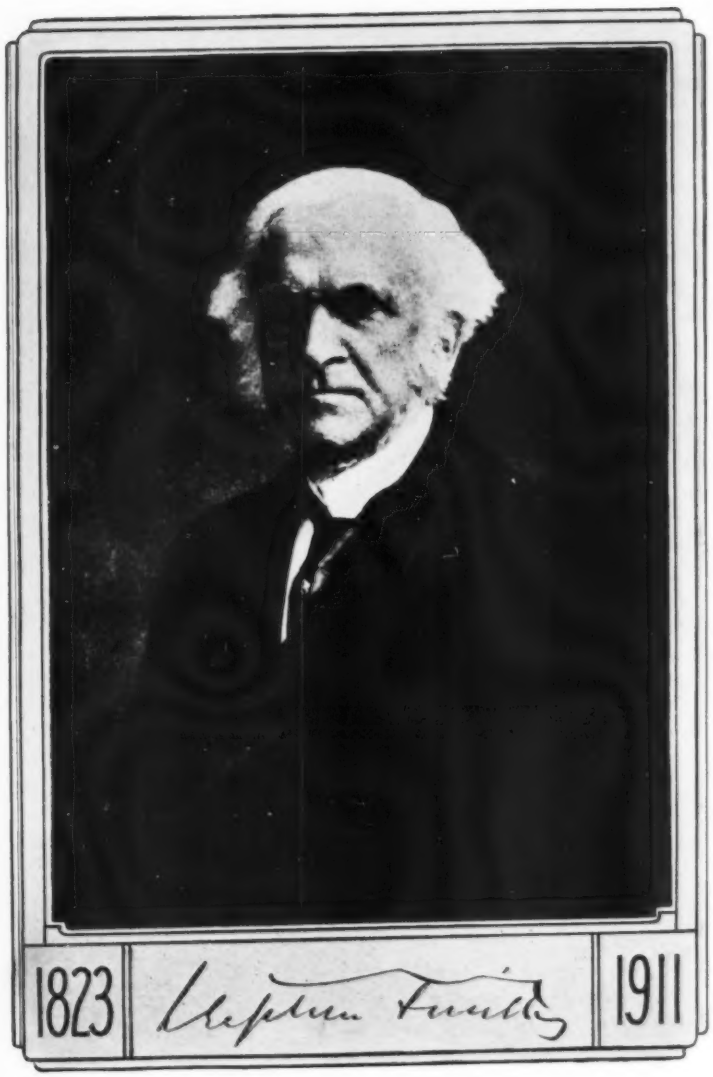
Next he turned to the study of the filtrable toxin which he and Felton had produced by growing the hemolytic streptococcus in blood. They completed and published a short paper on this subject, but much more work was planned to control and confirm their results. At the same time and before this he was working in a more leisurely way on the effect of diet upon the healing of wounds and had obtained some interesting results which were left in the form of notes from which Mrs. Clark has written and published his paper.

He was married at Portland, Maine, on July 9, 1917, to Miss Janet Howell, and his daughter, Anne Janet, was born on May 15, 1918. This was a year of extraordinary happiness for him. Since December, 1917, he had held a commission as first lieutenant in the medical reserve corps of the army and was very anxious to be assigned to active service, but the surgeon-general's office, recognizing the importance of his work on the streptococcus, supported it generously and kept him in Baltimore. In the autumn there came the epidemic of influenza and he was one of the many stricken. He appeared to recover from its first effects and returned to the laboratory for a day or two, but then developed a streptococcal pneumonia from which he died on October 13, 1918. His loss was among the greatest caused by that terrific epidemic.

Clark was a young man, prematurely slightly gray with an honest face and bearing which captivated everyone at once. He was so intelligent, so completely trustworthy and so efficient that there was never any hesitation in entrusting to him, when occasion demanded, the whole charge of the department, nor was there the slightest doubt of the propriety of his extraordinarily rapid advancement to the place of associate professor only three years after his graduation from the medical school.

ADMONT HALSEY CLARK.

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Aside from his undoubted ability in the routine work of such a department and his deserved popularity among the students and assistants who recognized at once his value as a teacher, he had a great talent for the investigation of the problems which interested him. Genius is a much misused word and can hardly be applied to Clark, because he was essentially well balanced and sane and went about his work upon a carefully devised plan which partook of genius only in that he had great enthusiasm, an almost unlimited capacity for concentrated work and a remarkable quality of efficiency. He worked early and late, even moving a bed into one of the rooms of the laboratory in the summer, when his wife and child were away, so that he could stay there continually and watch his experiments at night. When he constructed apparatus with much difficult glass-blowing and grinding of stopcocks, it worked. When he carried out a series of experiments to prove a point, they worked and there were few if any false steps. Foresight and rational judgment as to the relative importance of necessary evidence helped him greatly to advance. His problems were large and complicated and their solution involved long and difficult experiments—especially in the case of the pancreatic secretion, where he had to perfuse a surviving pancreas and a surviving and beating heart, analyzing the fluid from time to time as it passed; and it was only with very perfect apparatus, all of which he constructed himself, that it could be done. It was thoroughly good work and full of the most brilliant promise. He was only 30 when he died.

His interests were by no means limited to the laboratory. He loved the outdoor life, and all games and sports, but more especially, perhaps, the life of the woods with shooting and fishing. His vacations during his course at the medical school were spent working at summer camps for his uncle, Dr. Luther Gulick, and his honeymoon was a camping and fishing trip on Lake Temagami. He seems to have had the same skill in everything he did in the woods that he showed in the laboratory.

His loss is a very great one not only to us who knew and admired him, but also to science. He seemed destined to do great things.

His published papers were as follows:

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REMINISCENCES OF TWO EPOCHS—ANÆSTHESIA AND ASEPSIS

By STEPHEN SMITH, A. M., M. D., LL. D., New York

The development of an art is characterized by a succession of events each of which signifies progress. These events may, singly, appear unimportant, but, as Sir James Paget truthfully remarks, "Closely studied they are links in an endless chain of events leading to a higher development as we witness in the embryo." In this chain of events there occasionally occurs one which far transcends others in the radical and fundamental changes which it effects in the practice of the art under review. It stands a beacon light which illumines with ever-increasing brilliancy the pathway of the humblest practiser. Such an event creates an epoch—"A point of time from which succeeding years are numbered" (Cent. Dict.).

Baas, the eminent historian of medicine, regards epochs as the essential features of the development of an art and from an educational viewpoint urges that they be studied by every practiser. Impressively he remarks:

An acquaintance with the views and knowledge of epochs submerged in the shoreless ocean of time, frees the mind from the fetters and currents of the day with its often oppressive restraints, widens the horizon for a glance into the past, and an insight into the present of human activity, deepens the view for a comprehension of the ideas which guided the earlier and more recent physicians, and gives on the other hand to our daily professional labor a high consecration.

Though two of the most remarkable epochs in the history of surgery—anæsthesia and asepsis—occurred within my personal experience, it is unfortunately true that with the profession at large the views and knowledge of these great events have long been submerged in the shoreless ocean of time.

This general ignorance of the great events in the recent history of surgery is due to the failure of the schools to include in their courses of instruction a well-devised system of teaching the "views and knowledge of epochs." No department of science has a more interesting and instructive history than medicine, inasmuch as every advance tends to the betterment of the race. My experience as a teacher for many years emphasized the fact that students are not only greatly interested in historical incidents connected with the subject, but that those incidents proved suggestive to the memory when the subject was recalled in actual practice in later life.

Deeply impressed with the truth and moral significance of the historian's sentiments and their quite general application, it has occurred to me that it would be peculiarly appropriate to the present occasion if I recalled some of my experiences

and observations on the introduction of these two greatest epochs in the history of surgery.

ANÆSTHESIA

October 16, 1846

When I entered the office of Prof. Frank H. Hamilton, of Buffalo, New York, in May, 1847, as a student of medicine, anæsthesia was on trial. Though it bore the imprimature of the surgeons of the Massachusetts General Hospital, headed by the honored name of Dr. John C. Warren, several deaths had been reported during its use, which served to make conservative surgeons cautious. Prof. Hamilton was of that class and he resorted to anæsthesia only occasionally and in cases believed to be especially adapted to its use. This fact gave me ample opportunity to compare the old-time method with that promised by the new discovery.

The first operation without anæsthesia that I witnessed was so disquieting on account of the sufferings of the patient that I was nearly driven from the profession. Its cruelty was so shocking to my untrained nervous system that I begged to be excused from attending another operation, but the professor made merry of my sensitiveness, assuring me that the most successful surgeons had fainted at the first operation but that in the "long run" extreme sympathy for the patient made a cautious and conservative operator. The case referred to illustrates the ordinary operative proceedings in hospital practice at that time:

The patient was a workman from a shop and was suffering from a strangulated hernia. No other preparation was made than to remove his exterior clothing and sponge the surface over the hernia. The surgeon came in haste, put on a hospital apron and urged haste in bringing the patient to the table. Several strong-armed attendants were selected to hold the patient if he made resistance. With a conspicuous display of the knife the surgeon made his first incision with lightning rapidity which was followed by the violent screams and struggles of the patient and a volley of oaths. It required several minutes to place him again in position and meantime the surgeon, with knife poised in the air, awaited nervously an interval when he could cut twice in the same place. A second incision intensified the shrieks and efforts of the patient to escape from the table. All was now indescribable confusion, but the attendants succeeded in overcoming the patient now exhausted by his struggles and shock and at length the exciting tragedy came to an end, with all parties completely exhausted.

That this is not an overdrawn description of every day operations in the great hospitals of the country I will quote a reliable author's experience, the patient being a woman:

She is cheered by kind words, and the information that it will soon be over. . . . . She is enjoined to be calm and to keep quiet and still. . . . . But of what avail are all her attempts at fortitude! At the first clear crisp cut of the scalpel, agonizing screams burst from her and with convulsive struggles she endeavors to leap from the table. But the force is nigh. Strong men throw themselves upon her and pinion her limbs. Shrieks upon shrieks make their horrible way into the stillness of the room until the heart of the boldest sinks in his bosom like a lump of lead. At length it is finished, and prostrated with pain, weak from her exertions and bruised by the violence used, she is borne from the amphitheatre to her bed in the ward to recover from exhaustion.

The screams and struggles of patients submitted to operation, which we then heard and witnessed, were but the echo down the ages of those heard when the primitive surgeon first applied the "chipped-knife" to human flesh to remove the broken fragment of a war missile. There were screams and struggles in the home of Moses when Zipporah, his highbrow Midianite wife "Took a flint and cut off the fore-skin of her son" (Ex. iv. 24). There were abundant screams and struggles in the Jewish families when "Joshua made himself knives of flint and circumcised the children of Israel" (Joshua v. 3).

Pain and suffering was regarded as the chief obstacle to success in operative surgery from the time of that first operation with the knife or flint. Even Hippocrates, in lofty phrase, expressed the prevailing sentiment: *Divinum est opus sedare dolorem.*

Two methods of mitigating suffering seem to have been suggested to primitive surgeons, *viz.:*

1. Celerity of operation to diminish the time of suffering, and,

2. The discovery of an agent which would safely cause insensibility.

CELERITY OF OPERATION

Of these two methods the first was the most practical, as it involved no danger, and was, therefore, adopted at once. Successful celerity of operation required two conditions: (1) Such a variety of instruments as may be necessary to meet promptly every possible emergency; (2) Dexterity in the use of instruments. Fortunately the early Huns and Egyptians, by nature and training, were especially adapted to devise the instruments and use them dexterously—conditions necessary to success in celerity of operation.

In the field of invention the oriental excelled. Centuries before the Christian Era we have descriptions of instruments in familiar use by Hindus and Egyptians which in perfection of finish and adaptation to special uses are equal to the "kit" of the modern surgeon. For example, the forceps devised to extract the fragments of the rude missiles employed in the tribal wars were thus described by a contemporary writer:

They ought to be about nine inches long; their mouths be respectively like those of a lion, tiger, wolf, hyena, bear, elephant, cat, hare, antelope, crow, heron, dog, jay, vulture, falcon, owl, kite, cock, crouch, the bee, rat, mouse or bullock. Each half must be united to the other by a nail of the form of a lentil seed being bent inwards at the handles like the elephant-driver's hook.

There was also the same great variety of probes and tubular instruments each being designed to meet a special emergency during the operation. The following directions in preparation for an operation illustrate the care exercised by the primitive surgeon to render a rapid operation safe:

A surgeon contemplating to operate . . . . should first have ready the following: blunt instruments (forceps, etc.), sharp instruments, potential cauteries, horns, catheters, leeches, a dry

gourd, a cauterizing needle, stuffing materials, fat, milk, oil, string, board, bandage, honey, soothing decoctions, injections, lotions, fan, cold and warm water, a frying pan, able, steady and attached servants. During the operation let the patient be seated, who has taken very little food, offered sacrifices and made ablutions, with his face towards the East. The surgeon should stand with his face toward him and plunge his instrument after the proper incision until matter comes out, and withdraw it, avoiding vital parts, vessels, muscles, articulations, bones and arteries . . . . Boldness, rapidity of action, sharp instruments, operation without trembling, fear or doubt, are always praiseworthy of the surgeon.

As a "show-fad" dexterity in the use of instruments was at its climax when I entered the profession. At hospital clinics attended by students operators performed fantastic tricks with instruments often brandishing them in the air when about to make an incision. An amputation was a favorite occasion for these displays of dexterity. The Catlin, glittering for a moment above the head of the operator, was plunged through the limb and with one artistic sweep made the flaps or completed a circular operation. After several aerial gyrations the saw severed the bone as if driven by electricity. The fall of the amputated part was greeted with tumultuous applause by the excited students. The operator acknowledged the compliment with a formal bow. The clinics of these operators were as popular as theatrical performances and about as instructive.

Celerity of operation as I witnessed it, while accomplishing little in the mitigation of the sufferings of the victims of operation, often had very serious features. Wounds of blood vessels and nerves, puncture of viscera and similar accidents not unfrequently occurred in the clinics of operators famous for the display of dexterity and celerity. The movement of a struggling patient at the moment the operator plunged his knife resulted in wounding the femoral artery. Puncture of the urinary bladder and intestines, division of important nerves and similar accidents were reported from clinics. These accidents usually were the interesting feature of the operation, as they tested the ability of the operator to meet the emergency. The accident itself did not reflect upon the operator's skill but was attributed to the unfortunate movement of the patient at that critical moment when the surgeon was to exhibit his dexterity. Thus the tragedy that resulted in a coroner's inquest contributed to the reputation of the operator as a most skilful surgeon.

AN ANÆSTHETIC

Allusions to the use of "pain-killing" agents are frequent in medical history from prehistoric periods. In general their discovery has been accidental as in the case of gases from the earth. More frequently the narcotizing agent was found in vegetables, the poppy, the mandragora, belladonna, hyoscyamus, cannabis Indica, etc. Cutting operations without pain under the narcotizing effect of these vegetables are mentioned by many writers at different periods. Homer describes two operations in that picturesque style which suggests that he must have been present and witnessed them. He says:

Machon was summoned to remove an arrow which was driven through the belt of Menelaus, King of Sparta; he extracted the arrow from the well-fitted belt, but while it was being extracted the sharp barbs were broken; then he loosed the variegated belt and the girdle beneath and the plated belt beneath, which the brass-workers had forged, when he perceived the wound where the bitter shaft had fallen; having sucked out the blood, he skilfully sprinkled on it soothing remedies.

Eurypylus wounded with an arrow in the thigh called upon Patroclus to remove it. Patroclus, laying him at length, cut out with a knife the bitter, sharp arrow from the thigh, and washed the black blood from it with warm water. Then he applied a bitter pain-assuaging root, rubbing it between his hands, which checked all his pains; the wound indeed dried up, the bleeding having ceased.

The following prescription for making the famous anæsthetic of Theoderic (1278) illustrates the efforts to discover an anæsthetic:

Take of opium and the juice of unripe mulberry, of hyoscyamus, of the juice of the hemlock, of the juice of the leaves of the mandragora, of the juice of the wood ivy, of the juice of the forest mulberry, of the seeds of lettuce, of the seed of the burdock, which has large and round apples, and of the water-hemlock, each one ounce; mix the whole of these in a brazen vessel, and then in it place a new sponge, and let the whole boil, and as long as the sun on the dog-days, till it [the sponge] consumes it all, and let it be boiled away in it. As often as there is need of it, place this same sponge in warm water for one hour, and let it be applied to the nostrils till he who is to be operated on has fallen asleep and in this state let the operation be performed. When this is finished, in order to rouse him place another dipped in vinegar, frequently to his nose. Or let juice of the roots of fenigreek be squirted into his nostrils. Presently he awakens.

The story of the researches and efforts to discover a reliable and safe anæsthetic does not differ from that attending the introduction of all great epochs. Repeatedly the discovery was announced and the prize seemed won, only to be followed by a disappointment the more depressing because so often repeated. Indeed, these disappointments had so crystallized professional opinion against the possibility of discovering a safe and reliable anæsthetic that on the very eve of its announcement the most eminent surgical authority of the period, Velpeau, thus voiced the prevailing sentiment of the profession (1839):

To escape pain in surgical operations is a chimera which we are not permitted to look for in our day. A cutting instrument and pain in operative medicine are two words which never present themselves, the one without the other, in the mind of patients, and it is necessary for us surgeons to admit their association.

It is creditable to the profession that the chief obstacle to an earlier discovery of a safe and reliable anæsthetic was the fear of fatal results in making the necessary tests on human subjects. Rice, author of the "Trials of a Public Benefactor," remarks:

It is probable the deadly results which must have often ensued from their use, the long-continued depression which they exert upon the nervous system, the confirmed stupor and the congestions and other accidents which are so liable to follow, all conspired to prevent their use, or even examination.

The only interesting feature in the centuries of search for an anæsthetic relates to the incidents by which the inhalation

of nitrous oxide gas (laughing-gas) led to the discovery of scientific anæsthesia. In 1799, Sir Humphrey Davy, then an assistant in the "Pneumatic Institution" of Dr. Beddoes, Penzance, England, experimented with nitrous oxide gas and described in a familiar way its exhilarating and intoxicating effects. He even used it for the relief of pain in the head and teeth and finally suggested its possible use in surgical operations:

As nitrous oxide in its extensive operations seems capable of destroying physical pain, it may probably be used with advantage in surgical operations in which no great effusion of blood takes place.

The suggestion of Davy was so natural that it is surprising that nearly half a century elapsed before the subject again attracted attention, though nitrous oxide (laughing-gas) was in popular use for amusement in social circles.

The circumstances attending the actual employment of nitrous oxide to allay the pain of a surgical operation not only fulfilled Davy's prediction, but gave to our country the great honor of discovering a safe and reliable anæsthetic and also of placing anæsthesia on a scientific basis.

Dr. Crawford Williamson Long (1815-1878) of Danielsville, Ga., a graduate of the medical department of the University of Pennsylvania, was impressed, while attending an exhibition of "laughing-gas," with its power of causing a harmless delirium, and ventured to test its effects personally. In his performances under its influence he received a painful injury of his leg of which he was not conscious until he had recovered from the effects of the gas. Like Davy he became imbued with the idea that surgical operations might be performed without pain while a person was in this state of delirium. Long seems to have been a very unpretentious practiser of his profession in a small rural town quite remote from even the current medical topics. He engaged in general practice and performed all the surgical operations that came under his observation. In 1842 he first operated on a patient under the control of nitrous oxide and removed a tumor from the neck of a lady without pain. Subsequently he used this gas in his operations but did not think the method of sufficient importance to publish an account of it until the question of priority of discovery of an anæsthetic became the subject of Congressional inquiry on the petition of Dr. W. T. G. Morton, of Boston, 1847.

In 1844 nitrous oxide attracted the attention of Horace Wells, a dentist of Hartford, Conn., in the same manner it had Davy and Long, while being used as a "laughing-gas." Wells tested it by having a tooth extracted while under its influence and on returning to consciousness, exclaimed: "A new era in dentistry." He adopted it in practice and related his experience to Dr. W. T. G. Morton, a dentist of Boston and former partner in business. Morton was an enterprising young man who recognized the importance of the new treatment, if it really proved to be capable of accomplishing the objects claimed. He, therefore, thoroughly tested it and became convinced of its value in the practice of dentistry, the logical result of this conclusion being that it would prove equally valuable in the field of operative surgery. To test this question by high authority Morton applied to Dr. John Collins Warren then at the head of the surgical staff of the Massachusetts General Hospital. The day fixed for a trial operation was October 16, 1846. The operation was advertised widely and a notable gathering of the most distinguished members of the profession in Boston and vicinity was in attendance.

Prior to the date of the operation Morton had been advised by a chemist, Dr. Jackson, that sulphuric ether had the same effect as nitrous oxide and was more manageable. Accordingly Morton prepared to give this gas which occasioned a few minutes delay in his arrival at the hospital. This delay was construed by the skeptics in the audience as a complete failure of Morton to meet the test, and when he appeared a few minutes later he was greeted with derisive laughter. Even Dr. Warren had apologetically informed the audience that he had little faith in the alleged anæsthetic.

The operation, the removal of a vascular tumor of the neck, was a complete success. A profound silence fell upon the witnesses of a great epoch in surgery as Dr. Warren declared in homely phrase, "Gentlemen! This is no humbug." This announcement, heard around the world, ushered into human history the great epoch—ANÆSTHESIA—freedom from pain in the practice of operative medicine.

ASEPSIS

1867

The discovery of a safe and reliable anæsthetic seemed to cut the cords which restrained the progress of operative surgery and this branch of practice went forward in leaps and bounds. Medical periodicals were filled with descriptions of new, unheard of, and even unthinkable operations, and the clinics became interesting for the novelty of the operations and the perfection of details, now so much more carefully completed.

THE ANTISEPTIC PRINCIPLE

1867

But important as was the reform in the manual of the operation, it was painfully apparent that in the final summary of results the mortality of operated wounds had not diminished. The chief element of disaster, suppuration, still remained in full force and determined by its relative intensity the final result. Of this fact I had an opportunity for ample experience. On entering the Bellevue Hospital Resident Staff (1850) my duty as the junior member was to carry the "pus-pail," the receptacle into which the senior surgeons placed the pus-saturated dressings. Two and often three times daily he had to renew these dressings, each change attended by great suffering and exhaustion. I vividly recall our painful disappointment on witnessing the gradual failure of the vital powers of patients with such an outflow of pus. Daily the visiting surgeon examined the pus to see if it was not becoming "laudable" and pressed iron tonics, but the final result was general infection.

From the time of Hippocrates there were two schools of surgeons based on the question of the treatment of wounds with and without pus. Although pus was almost universally present in healing wounds, still there were occasional instances where the wound healed without any discharge, but remained dry throughout the process. This incident gave rise to two methods of treatment, the "dry" and the "wet," the former being our healing by "first intention," and the latter by suppuration or granulation (second intention). Though the intuitive genius of Hippocrates led him to teach healing by the "first intention," as the correct practice, he was violently opposed in the schools of Greece, and the "wet" treatment prevailed, its advocates regarding it important even to apply irritating dressings when pus was not freely secreted. These two schools continued to our time, the "wet" method being generally taught in the colleges and practised in the hospitals. Pus was not regarded as injurious to the wound except when of unhealthy quality and it was the quality, not the quantity, that interested the surgeon. Good pus was thick like cream and was called "laudable pus"; it was thought to indicate healthy healing. Practically we had a continuation of the old controversy of the healing of wounds by "first intention," the "dry method," or by suppuration, the "wet method."

Lister's series of experiments by which he demonstrated the element in pus which renders it prejudicial to the healing of wounds, and the discovery of an effective remedy by which that element can be rendered inert from the moment of operation, are the most brilliant in the annals of science. Impressed with the fact that he had a mortality of 45 per cent in his cases of amputation, though great care was exercised to protect the wound, his mind recalled Pasteur's theory that microorganisms are the cause of putrefaction and that in his observations putrefaction was present only when there was suppuration. He at once began experiments to test the truth of the theory of Pasteur by employing such agencies as he could command to destroy any germs present and still not harm the wound. He was finally led to the use of carbolic acid which proved satisfactory.

Lister began his experiments in 1865 and printed his first paper entitled, "On the Antiseptic Principle in the Practice of Surgery," in 1867. No one but a contemporary of that period can realize the storm of criticism and ridicule which greeted the author of that paper. He was accused of not being original in his work; of not obtaining better results than the old method of practice; of rendering operations tedious; of employing childish and ridiculous apparatus and dressings.

Lister answered his critics by the performance of new and more incredible operations without pus or fever and in the meantime improved the details. His reported excision of a knee-joint, 1878, and wiring a fractured patella, 1883, without suppuration, brought to a climax the amazement of older surgeons at his pretensions. But what appealed to the elders as recklessness inspired the juniors with a commendable desire to test the truth of his statements in actual practice. I introduced the practice into the wards of Bellevue Hospital greatly to the disgust of many of my colleagues who refused even to visit the wards where the patients were under treatment. I had the satisfaction, however, of a visit of Mr. Lister himself, while on a tour in this country, who generously commended my work and in his autobiography gives me the credit of introducing asepsis.

On visiting Lord Lister at his London residence in 1894, I found him quite pessimistic as to the then state of asepsis. He remarked that he believed true asepsis was rarely practised. "Why," he said, "I was in Berlin a few days ago and at the urgent request of friends attended the clinic of a noted aseptic surgeon. All his methods were excellent but on becoming confused in the operation he stopped, scratched his head, and completed the operation without sterilizing his fingers. That was an infected wound and its suppuration will be attributed to the failure of asepsis."

On relating this incident to a former house surgeon to Lister's ward while he was experimenting with different agents, he said: "Lister was very much subject to perspiration especially when intently engaged in an operation, and I have often seen the sweat of his face fall into the wound without attracting his attention." Lister's great success, even under such unfavorable conditions, depended, probably, upon the thoroughness with which he finally applied disinfectants, for he dwelt especially upon that feature of aseptic treatment.

ANÆSTHESIA AND ASEPSIS

1867

With the introduction of asepsis into practice the art, operative medicine, became a true science. The entire process was governed by rules which ensured success. Compare Lister's statement that his best results in amputations showed a mortality of 45 per cent in 1864-1866 by the best methods then in use, with a recent report of a hospital in New York that in fifty consecutive cases of laparotomy, involving many varieties of intra-abdominal affection, 100 per cent of the patients made a good recovery.

It was very gratifying to me to learn of the following incident which occurred at the Bellevue Hospital recently where pus reigned supreme prior to 1867. A professor in one of the medical schools wished to exhibit a specimen of fresh pus to his class and naturally directed the messenger to apply at Bellevue Hospital. On making his errand known he was informed that pus in operation wounds had long since disappeared from the wards. Prior to the year 1867 healing by first intention in that hospital was neither expected nor sought by the surgeons. One of the most distinguished operators merely brought the surfaces of the wound together with adhesive strips and placed the wound in such a position that the pus would flow into a vessel, thus avoiding the necessity of frequent renewal of the dressings.

Now all is changed. Healing by first intention is always sought and the presence of pus in operation wounds is a severe reflection upon the care and skill of the staff in charge. But perhaps the greatest and most beneficent result of the im-

proved methods of treatment in operative surgery in this anæsthetic-aseptic era is the rapid convalescence of patients. The operation which formerly was the beginning of the end, owing to the exhaustion due to the suppuration which ensued, is now the beginning of a rapid convalescence. The feeble, nervous sufferer whose heart nearly ceased its action on the thought of an operation now approaches the operating room with a firm step, a normal pulse, and mounts the table with a smile. As operations under the old-time system were illustrated by the description of concrete cases, the vast improvement effected by the combined methods of anæsthesia and asepsis will be most thoroughly appreciated by a similar report of cases treated according to the principles established by these great epochs.

A young woman, aged 18, had suffered from a suppurative disease of the knee-joint five years, and was reduced in vitality to a helpless state. Her fear of an operation rendered her nervous system so sensitive that she had attacks of fainting when an operation was mentioned in her presence. And yet delay of an operation seemed more dangerous than its possible fatal results. A medical friend suggested the preparation for the operation be made in an adjoining room and he would visit her as chaplain and induce her to inhale chloroform to unconsciousness when she could be quietly removed to the operating table.

The ruse worked admirably. The patient was delighted with the perfumery, as the physician called it, and required but three or four inhalations to become insensible. Excision was performed, requiring an hour to complete it and its aseptic dressings, but her pulse continued good under the influence of hypodermic injections of heart stimulants. For several days she was in ignorance of the operation and was surprised that she had no longer pain in the knee but occasionally in her toes. One morning she saw a spot of blood on the sheet over the knee and was greatly alarmed as she had been told there was danger of fatal hemorrhage. On being assured that there was no danger and that the operation had been performed and she was recovering, she became frantic with joy. A vigorous appetite now developed and with freedom from pain and refreshing sleep, her rapid recovery was daily noticeable. The first dressing made was on the twenty-ninth day and there was only slight yellow staining but no pus. She had gained eight pounds in weight.

The following incident led me to adopt a method of anæsthetizing very feeble patients which has proved very serviceable. I was aiding a colleague in an operation for cancer of the breast on an old lady who was very fat, with a feeble intermittent pulse and nervous excitement. She had been prepared in the usual way with purgatives and simple diet. She had taken but little ether when her face became purple, her pulse disappeared and after a struggle to restore her she was pronounced dead.

It happened that I had a duplicate of this case on which I was to operate on the following day. I was so shocked by this experience that I delayed the operation and studied the situation. The result was the conclusion that probably these patients' feeble and intermittent heart-action was due to overlaying and interstitial fat and required supporting rather than the depressing treatment then employed. Though this indication could be met by hypodermic heart stimulants I recalled two facts that determined my course, *viz.:* (1) Larrey, in his memoirs of the Napoleonic wars advised operations on soldiers while they are drunk, for they neither fear nor feel pain, and (2) hot milk is a quick nutrient and sustains a weak heart. Here were the remedial agents which my patient required to prevent fatal collapse.

After preparatory treatment I directed that at 8 o'clock on the day of the operation which was at 3 o'clock, the patient should receive one ounce of hot whiskey in a glass of hot milk, and the same must be repeated at 10 and 12 o'clock unless she was much disturbed. On visiting my patient at three o'clock on the day of the operation I found her in a most satisfactory condition. She had not required the stimulant the third time, having become quite excited about the details of the operation which had taken fantastic forms in her enlivened but disordered imagination.

On entering the ward she greeted me with some affectionate terms, expressed her delight that the operation was about to be performed and wished she could see the medical students present. Her face was flushed, eyes suffused, skin warm and her pulse full and regular at ninety-six. She came under the influence of the anæsthetic without a struggle and required an amount estimated at one-tenth that ordinarily given, the whiskey having already secured partial anæsthesia as Larrey suggested when he ordered wounded soldiers to be operated on while drunk. The pulse remained at ninety-six during the time occupied by the operation and the application of the aseptic dressings. She made an unusually rapid recovery, the pulse continued at ninety-six for several days; her appetite became vigorous; her happiness that the operation was over was extreme. But one dressing was employed and when it was removed there was no sign of pus and only the yellow staining of serum.

During the many years that I have used this anæsthetic, hot milk and whiskey, I have not seen a patient fear an operation, nor suffer from shock or collapse.

I trust these desultory reminiscences of the introduction of the two greatest epochs in human history may lead us to a proper appreciation of the labors, trials and skill of the surgeons of the pre-anæsthetic period, who amid the heart-breaking screams and uncontrollable struggles of patients devised and successfully performed the great operations which adorn the annals of surgery.

There is a profound truth in the remark of the historian, that "such knowledge widens the horizon, for a glance into the past, and an insight into the present of human activity, deepens the view for a comprehension of the ideas which guided the earlier and more recent physicians, and gives on the other hand to our daily professional labor a high consecration."

NOTES ON THE GROUP OF SYMPTOMS DESIGNATED AS EFFORT SYNDROME

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A little less than three years ago, when the stage was being set for the comedy entitled "The Second Mexican War," the writer was called into military service and assigned to the duty of physically examining the Maryland militia before its federalization. It was his first experience in the examination of large numbers of men and several interesting lessons were forthcoming which were later to prove most valuable. In the first place, an opportunity was afforded to appreciate the wide range of what may fairly be called the norm of the cardio-vascular system. The prevalence of apical and conus systolic murmurs, the presence of short, scratchy, systolic murmurs near the sternum, the intensity of the second sounds at the base of the heart and their relation to age, third sounds, presystolic sounds, sharp clicks heard only in systole near the apex of the heart, the relation of posture to the position of the apex—all, with many other variations, are subjects well worth individual discussion, which may be dismissed here with the remark that for a proper valuation of such findings a competent knowledge of the normal is indispensable. Secondly, the variation in the pulse-rates of healthy individuals was noteworthy, and the dependence of this rate upon the condition of the mind and body was emphasized. Thus, tachycardia might be found in certain healthy young men who, having been told by a physician that they had heart trouble, did not believe they could pass the examination; or, again, men suffering from venereal infection and fearing its discovery might show an increased pulse-rate. Confirmed neurasthenics, a few men who had been forced into service by the jibes of their friends, those who were doubtful of their right to expose dependents to the charity of the world, any of these soldiers might appear for examination with a rapid heart. The association of certain organic physical diseases generally of an infectious character with tachycardia was constantly exemplified in the men with early or outspoken tuberculosis, bronchitis, or even with furunculosis.

A mental note was made of the high percentage of infected gums and carious teeth among the otherwise healthy and well-developed farmers, while the underdevelopment of the clerk group of the city men was conspicuous. One company having been recently organized in the vicinity of the mobilization camp was still below the numerical standard, and on the day before the examination, its officers, dependent for their positions upon the acceptance of the company by the army, collected a lot of young boys to supply the deficit. These lads claimed 18 years, but many of them were evidently younger.

During the three weeks of my duty at this camp, quite a number of men appeared at the hospital for re-examination because they were unable to perform their daily tasks. Many were young boys, a bit shaky, a little short of breath, with acro-cyanosis of the extremities, sweating freely, and often complaining of sharp pains which they localized in the precordial region. A second physical examination, less hurried, disclosed nothing further of importance and it seemed that one was witnessing the attempt of a youth to do a man's work and the subsequent natural exhaustion. At the same time, others, many of whom had been noted as underdeveloped on the first examination, returned with similar complaints—they also had given out.

The rest of the summer was spent at the Artillery School at Tobyhanna where the Yale batteries and a few national guard organizations were training. During this period a few men were brought up for examination because they had not been able to stand the hard work—they had become irritable, did not get along with their fellows, and had lost weight. During the examination, they were apt to be a little shaky, the perspiration would roll down from their arm-pits, although the weather was comfortably cool; some degree of tachycardia was generally noted, and in response to slight exercise the rate would become excessive. Some of the soldiers had, in the course of the summer, slight attacks of tonsillitis or average colds of a few days' duration. It was interesting to follow these men. Whereas some of them went back to duty after a few days in the hospital and soon forgot their illness, others would remain below par for several weeks and have difficulty in doing the work that had caused them no discomfort before they had become sick. A few men showed a sensitive vago-sympathetic balance, and were apt to faint in the ranks during a protracted muster. The different vaccinations were administered at this camp, and it was not infrequent to have in line husky, strong soldiers who were obviously afraid—the skin cold and clammy, with rapid heart and panting respiration. Others, blatantly brave, would faint from the prick of the needle.

The result of the summer's work was an appreciation of the infinite variations that are to be found among individuals—the variation in the sensitiveness of their reflex arcs, the variations in their bodily and mental reaction to physical and psychical trauma and so forth. Indeed each individual is so different in his bodily make-up and in his reaction to outside stimuli that the normal is very difficult to delineate and standardization becomes practically impossible.

Some of you have taken part in athletics at college, and will recall personal experiences similar to those that the writer himself remembers. Often, immediately before a football game or his race in a track meet, he suffered what now sometimes comes back in the form of a nightmare. Although, in excellent physical condition, he would go out on the field all atremble, with his heart racing and trying to beat its way through the chest, breath short and insufficient because of

a suffocative band that seemed to constrict the lower thorax and to prevent the ingress of air. Occasionally, after some particularly inspiring speech from a well-wishing alumnus, he would go out sweating profusely, with involuntary micturition, and even crying. The actual start of the game was always sufficient to bring back the normal functioning of the body. Again, you may remember your own condition or have seen others at the end of a short period of extreme bodily exertion, as at the end of a hard race for a quarter of a mile. Some men become pale with slight bluing of the mucous membranes, the cheeks sunken, trembling, occasionally fainting; others quite purple with puffed cheeks, watery eyes, nauseated even to vomiting, and often with blood-tinged sputum—both groups representing the signs of acute fatigue, the result of extreme exertion.

How often in the course of a wearing season does the coach tell one of his men that he is overtrained! The man is irritable, has lost weight, is not sleeping, his pulse-rate is sensitive to slight exertion, he is constantly sweating in cool weather, his general physical strength is decreasing, and he cannot approach his average record; while his team-mates are doing well and are improving under exactly the same work. Rest and a change of scene may soon return the overtrained man to his former condition, but the trainer has been to blame for the loss of time; he was treating all his athletes according to one standard, and this cannot be done with success. It is generally known that the captain of an athletic team is rarely so good during his tenure of office as he was the season before when he did not have to worry about the condition of the whole team in addition to performing his own individual work. It may even become necessary to send such a man away to continue his training by himself.

Experience in the training of track men develops the opinion that there are two outspoken types of athletes with numberless gradations between, the one capable of supreme concentration of energy for a short period of time, the dash man, the other slow-going and very resistant to fatigue; the former nervous, high strung, the hyperthyroid type, the latter steady and plodding, a successful long-distance runner. The training of the two groups should be quite different. The training of the sensitive dash man is always difficult. His work reflects his mental attitude, and the worry of a failure in recitations will be recorded by the reduction in his speed, whereas the phlegmatic distance runner plods along comparatively uninfluenced by his surroundings. Reverse these men, and the long-distance man is a failure in the sprints and the dash man will not only be unsuccessful in his new work but may also develop typical signs of *effort syndrome*.

One more observation from the field of athletics. Perhaps some of you have gone back some time after you left college, and have been asked by some enthusiastic coach to change your clothes and line up on the scrubs or to take out the hurdlers and show them some of the fine points of that race. All of us hate to admit that we are getting old, and perchance you have tried to do what you could. Just one such attempt may teach you the symptoms of effort syndrome and, in that event, you become very sympathetic towards individuals suffering with this condition. The writer attempted such work within a few years of active athletic participation, at a time when he was in fair condition from tennis playing. Pride kept him from acknowledging failure before the crowd, and he kept up his unusual exercise for an hour or so; but for days afterwards he felt the effects—not only stiffness, but shortness of breath, untoward pulse acceleration, trembling, and precordial pain on slight exertion.

The same general reaction may be experienced during convalescence from even a slight infection. Those of you who have had influenza appreciate the long period that may elapse before you can comfortably perform your daily tasks. A physical examination may reveal no abnormality, but short walks are very tiring, and any continued mental labor is exhausting. Protracted asthenia after tonsillitis or slight colds is not infrequent in the medical dispensary.

It is an interesting fact, in this condition, that, bar an untoward accident such as an embolus or a ruptured valve, athletes or patients convalescent from acute disease never die during the period of activity. The will-power of individuals varies, and some men endure discomfort and withstand bodily punishment to a greater degree than others, but the limit in every case is always short of complete exhaustion of any organ of the body. This fact is intimately associated with some sort of protective mechanism of which the nervous system plays an important part and in which the resulting physical signs are manifested to different degrees as well as in different ways.

These observations serve as examples of conditions in which the symptom-complex called *effort syndrome* may obtain. Suggestions are made which point to a similarity of these signs to those manifested by the body in fear and in acute exhaustion.

In June of 1917, the writer was sent with The Johns Hopkins Unit to France where he was stationed for eight months in a base hospital. Here several facts were generally appreciated. The preliminary physical examination of the early recruits had been unsatisfactory, and for a while many of the patients were men who should never have been admitted to the service. There were not a few examples of dementia præcox, constitutional inferiority, grave neurasthenia, besides organic physical diseases. Many of these men showed, in addition to the signs peculiar to the individual organic disease, symptoms comparable to those already described. Then there were soldiers who had had no previous training, and who broke down under the strenuous physical demands which were especially exacting in the face of the poor housing facilities and unsatisfactory hygienic surroundings. There were cases of tuberculosis, infectious arthritis, horrible teeth, old infected tonsils, and similar chronic infections, and many of these men showed the same excessive reaction to exercise. Many soldiers who had come to base hospitals with acute diseases such as pneumonia, acute bronchitis, or acute tonsillitis and who had been discharged apparently well, had returned to the hospital with symptoms of fatigue on slight exertion. These symptoms were very apt to be referred by the battalion medical officers to the cardiovascular system because of the rapid heart or the shortness of breath. Moreover, the lack of knowledge on the part of

many medical officers of the range of the findings in the normal heart, caused, in face of symptoms so commonly associated with cardiac disease, a pathological interpretation of conus murmurs or third sounds, and the patient would be told that he had heart disease. After the occasional man suffering from organic disease had been weeded out and disposed of, and the better diagnosis of effort syndrome made, it was found that there was no satisfactory arrangement for the treatment or disposition of such patients. As the demand for acute beds increased, some of them would be sent back to duty, while others would be transferred to other base hospitals where they would lie around for a few weeks and then again be put on the active list. Or they might again be regarded as sufferers from organic heart disease, be put to bed and given digitalis. After this treatment, they would generally get out again with their symptoms made worse, which more than ever convinced the patients that they were suffering from heart trouble which could not be cured. Such a belief always militated against the patient being willing to take active exercise.

When the medical consulting staff was established under General W. S. Thayer, an effort was made to rectify this unfortunate condition and thereby avoid the resulting vicious circle in transportation, as a consequence of which these soldiers were spending most of their time in transit to and from the front line. Convalescent camps were to be established where treatment could be carried on intelligently, and where more protracted study of these patients might be made. At this time the writer was sent to England where he was attached to the British Military Heart Hospital which was doing excellent work under the direction of Dr. Thomas Lewis. Here were to be found the most extreme types of effort syndrome listed under the British medical nomenclature—disordered action of the heart. Dr. Lewis's work was fundamental. He showed that graduated exercises furnished a method for the functional testing of individuals and their subsequent classification for different degrees of physical work. This treatment, furthermore, proved to have an important curative value, so that he sent many of his patients back to front-line duty. The British medical corps was unfortunate in not having a psychiatric division, and, indeed, there was no special hospital in England for the treatment of psychoneuroses. A patient was either demented, whereupon he was sent to an insane asylum, or he was mentally correct. Such treatment as could be accorded the functional mental disorders was, as a rule, only that found in any base hospital conducted by a busy staff which must first meet the demands of the acutely ill. The treatment for the psychoneurotics was just the same as for the cases of effort syndrome, but this lack of differentiation furnishes one of the explanations of the high percentages of D. A. H. cases among the British. Dr. Lewis was preaching the gospel throughout England that these patients were made worse by being put to bed and being given digitalis; but it was slow work, and the general lack of knowledge as to what physical signs of the cardio-vascular system could be classified under the normal was a great handicap to overcome. Moreover, England was short of man power; underdeveloped men had to be used for front-line duty, convalescence from acute infections was apt to be too short, and underaged as well as overaged men were constantly exposed to the demands of campaigning. Again, his hospital was well away from the firing line, and, as a result, his patients had passed through a series of base hospitals before he saw them, and by that time they had become thoroughly convinced, from their diagnosis cards and from information obtained from different medical officers, that they had definite heart trouble, which, to their minds, was incurable. Certainly the subjective symptoms strengthened that conception, and, moreover, four years of warfare had deprived some of them of any excess enthusiasm for staying in the army if there were any fair way of getting out.

Dr. Lewis and his staff had made many careful studies of their patients.[1] Controlled pharmaco-dynamic tests were employed with the following results: Atropin showed no difference between patient and control. Apocodeine generally gave a greater pulse-rate rise and there was a more marked cutaneous reaction in the patient group. Amyl nitrite had the same result. Pilocarpin produced more marked reaction among the patients. Digitalis had no more power to control the pulse-rate of the patients than of the controls, and the subjective symptoms were uninfluenced. Adrenalin, on the other hand, showed that the patients had a definite susceptibility to this drug so far as subjective symptoms go, but the rise in pulse-rate and blood pressure was about the same in the two groups. Another interesting study showed that the patients were apt to require a longer period after measured exercise before their pulse-rate lost its increase—five minutes, often, as compared to two minutes in the average control. X-rays and electrocardiograms showed no essential difference in the two groups. All in all, the work suggested that the disorder had to do with the peripheral nerves rather than with the central nervous system, and there seemed to be a hypersensitiveness of the sympathetic with no change in the vagal system.

After a stay of two months in England, the writer was sent back to France and assigned to duty at Convalescent Camp Number Two. This camp was the convalescent section for a large base hospital group, and had a capacity of 2000 patients. The work was very active and, at first, was complicated by the considerable amount of organization that was to be expected in the establishment of a new system. Graduated exercises were instituted under military discipline, so that each patient was tested as to his capacity for work and was not discharged to front-line duty unless he was able to perform comparable work. Each patient was carefully studied during his stay and any indicated laboratory tests were made. Moreover, a follow-up system was instituted which enabled us to arrive at definite conclusions about the method of treatment, and controlled the results.

The writer has summarized the first 5000 case-histories, and some of the findings have a direct bearing on the discussion of effort syndrome. Ninety-one per cent of all patients were sent back to full duty, and 3 per cent were returned to base hospitals for operation or for treatment which would probably later

admit their discharge in Class A. About 1½ per cent of all cases were reclassified with the diagnosis of effort syndrome. This group was made up in equal proportions from patients with varying diagnoses on admission. That is, the effort syndrome cases were found just as frequently among patients who had had influenza or pneumonia, as among those who had been gassed. Every patient was especially studied for symptoms of hyperthyroidism. Only three cases of exopthalmic goitre were found among the 5000 under discussion, and, outside of these, only an occasional soldier showed struma, adenoma, diarrhœa, or any eye signs beyond a slight von Graefe. Nearly all the effort syndrome group showed a slightly accelerated pulse-rate, excessive sweating, restlessness, and dermatographia. Further signs that might be ascribed to hyperthyroidism were not conspicuous among these men.

The majority of patients on admission, especially those who had been suffering from an acute infection, showed what might be called effort syndrome. But these signs, in most instances, disappeared after treatment, and rarely reappeared after the patient's return to duty. In this connection it is interesting to compare the duration of the patients' stay in hospital before and after the establishment of convalescent camps. The functional test afforded by graduated exercises proved that, in general, the period which had been allowed in base hospitals for convalescence was too short. The average case of pneumonia needed eight weeks instead of the five permitted before discharge; mumps required 39 days instead of 18; herniotomies seven weeks instead of three and a half, and so forth. In all probability it was to this prolongation of the period allowed for convalescence that such favorable reports from the "follow up" system were due.[2]

Of these 5000 cases the diagnosis of anxiety neurosis was made in 192. It would lead far afield to enter into a discussion of this disorder and its relation to fear; however, many of these patients showed symptoms quite similar to those of effort syndrome. The recovery of these soldiers was very slow, necessitating, on an average, seven weeks. They needed much more individual care than did the general run of patients, and the success of the treatment depended, in large part, upon the ability of the individual ward doctors to handle psychoneurotics. A good many of them certainly had a psychasthenic basis, or at least had a weakened will-power. But there, again, the extremes of normal are hard to mark out, and, moreover, the degree of psychic shock had been extremely variable. One hundred and sixty or 83 per cent were sent back to front-line duty and 4 per cent were returned to the base hospitals for operations or because the patients had contracted some acute infection. That is, 13 per cent were reclassified as compared with the general percentage for the 5000 cases of 6 per cent reclassified. On discharge many of these reclassified men showed symptoms of effort syndrome in varying degrees. Of the 80 patients admitted with the diagnosis of exhaustion, 95 per cent were sent back to the front lines. They had required an average of six weeks in the hospitals and camp, but after recovery they "carried on" normally in their original commands. Many of this group had shown signs of effort syndrome on admission.

Not far from our camp was a hospital devoted entirely to the treatment of war psychoses. As a result of exchange visits, the physicians of both places learned to appreciate the similarity of the symptoms to be found in both establishments. In many instances we agreed that the original diagnosis had depended in large part upon the specialty of the physician who had first seen the case—the psychiatrist favoring the diagnosis of anxiety neurosis, the cardio-vascular man, effort syndrome. At first the psychiatrists had claimed, and probably correctly, that their specialty was fundamentally concerned, but they became less insistent that such patients should be sent to their hospital when they came to appreciate that we all were treating these soldiers in much the same way. Indeed, after the armistice, when the psychiatrist in charge had issued an order that no cases of war psychoses should be sent to the states, and when the disposition of these patients became a problem, the psychiatrists began to unload on us and we received numerous soldiers from their hospital with the combination diagnosis of (1) effort syndrome; (2) anxiety neurosis. We rather felt that this order of diagnosis should have been reversed, but such a change would have only started a vicious circle of transportation which, of course, would have been foolish. It seems fair, then, to assert that individuals vary as to their power of resistance to psychic trauma, and that many individuals after prolonged psychic trauma may show signs of effort syndrome.

With this accumulated information, it is interesting to speculate as to the cause of effort syndrome. Many investigators believe that these patients are suffering from a definite disease, and are endeavoring to find a single etiological basis. Probably such efforts will never be successful, and it seems rather that effort syndrome is a name for a medical wastebasket whose contents must be carefully sorted into etiological groups. Some of these groups are very easily understood—those with a definite physical basis. Under this caption appear convalescents, both those from recent acute infections and those whose original period of convalescence was so short that they were subsequently returned to the hospital for continued treatment. Effort syndrome after exhaustion seems reasonable, as does that in association with actual physical disease—tuberculosis, tonsillitis, exopthalmic goitre, and so forth. Another sample is furnished by hyperthyroidism where, in addition to the symptoms of effort syndrome, there should be further signs incriminating the thyroid—diarrhœa, struma, adenoma.

It is possible to conceive of psychical conditions which may induce the symptoms of effort syndrome. Acute fear gives such symptoms; patients who are constitutionally inferior, those exposed to prolonged psychic trauma, perhaps another group—individuals the victims of chronic fear—all of these patients might be regarded as supplying an etiological basis fairly well understood. It is certainly true that men, who had been on the front-line for a year with no discomfort, might receive a culminating psychic shock that would induce the onset of their symptoms.

There are, however, many cases which are not so easily understood, and do not seem to belong to any of these different etiological groups. It is possible that we are here dealing with

the training of track men on a large scale. Just as putting all athletes to running long distances will develop the symptoms of effort syndrome, so submitting large numbers of young men to the protracted training of a recruit, where individuality is entirely disregarded, will show a number of men who give out. The phlegmatic distance man and the nervous dash man are fundamentally different people, with different bodily make-ups. The gradations between the two extremes are limitless.

To designate diseases, names are employed. These names describe maladies which are different, with different etiology, different pathology and different courses. If this view as to the multiplicity of etiological factors is conceded, then effort syndrome is no more a correct diagnosis than is jaundice or tachycardia. To all the names for this condition, which, by the way, have been applied by cardio-vascular specialists rather than by internists, to these names—irritable heart, disordered action of the heart, neuro-circulatory asthenia, effort syndrome—it would be foolish to add others. But it does seem worth while to endeavor to go back of a prominent symptom and to attempt a primary diagnosis, and allow the symptom-group to be secondary. At our camp, where we all believed in the multiplicity of causes, such effort was made, and more and more we employed such combination diagnoses as the following: Protracted convalescence, effort syndrome; exhaustion, effort syndrome; psychasthenia, effort syndrome; anxiety neurosis, effort syndrome, and so forth. It is this reason which prompted the choice of a title for these notes, not effort syndrome, but the group of symptoms designated as effort syndrome.

Just a word as to the pathological physiology of this condition.

What is the actual construction of this protective mechanism? It is not yet evident. Perhaps explanations will be forthcoming some day from the physiologists. The processes involved in effort syndrome may well be related to those in fatigue or fear. Barcroft has shown that patients with effort syndrome are not benefited by the oxygen chamber—a treatment with the purpose of oxydizing any fatigue products that may have been accumulated in the body. Nor have we, as yet, any proof that, as in fatigue, there are definite chemical substances concerned. Other studies suggest that the endocrine glands play a part, and different hypotheses have been evolved on this basis. Dr. Cannon's conception of the mechanism of fear[3]—an adrenalinæmia due to nervous stimulation of the adrenal glands—is most attractive, and it is very unfortunate for our peace of mind that his hypothesis has not been substantiated by the work of other investigators. In this connection it is important to remember that, while exhaustion in some way is brought about by the accumulation of metabolic products together with a depletion of energy producing substances, the initial action of these same substances is distinctly physiological and provides an increased capacity of the body for work. The demarcation between the helpful and the harmful is not sharp. In the same way, it is not at all impossible that the symptoms of effort syndrome are the result of a perversion or an overaction of a normal bodily mechanism.

It is hardly worth while to enter into a discussion of the thyroid and its relationship to effort syndrome. It is all too speculative. But it is a fact that nearly everyone has started out in their work with these patients with the idea that the thyroid was etiologically concerned. Excluding the definite cases of exopthalmic goitre and cases of hyperthyroidism with actual localizing symptoms, it may well be that the thyroid is concerned with the production of some of the symptoms of effort syndrome, but there is no investigation yet forthcoming that has proved it to be fundamental. Treatment, directed to this special organ, would be symptomatic treatment, and, in a way, would be comparable to the extirpation of the liver in cases of pneumonia that show jaundice. The jaundice, in great part, would be cured, but there would be no improvement in the pneumonia.

While it may be that the importance of effort syndrome has been overestimated, and although it is possible that such a diagnosis is often a confession of failure on the part of the examining physician, the discussion is valuable. From it comes a conclusion which has been well expressed by DaCosta.[4] "In bringing this inquiry to an end, I may be permitted to point out what I believe to be its chief interest and value. To the medical officer it may be of service as investigating a form of cardiac disorder which every severe or protracted campaign is sure to develop. And, from a military point of view, further, it enforces the lessons, how important it is not to send back soldiers, just convalescent from fevers or other acute maladies, too soon to active work. It suggests that their equipments be such as will not unnecessarily constrict, and thus retard or prevent recovery; that recruits, especially very young ones, be, so far as practicable, exercised and trained in marches and accustomed to fatigue before they are called upon to undergo the wear and tear of actual warfare, and it exhibits some of the dangers incident to the incessant and rapid manœuvering of troops. True, on a movement executed on the double quick may depend the issue of a battle; a forced march may determine the fate of a nation; and the time can never come when purely physical considerations can forbid either one or the other, or dictate how often they may be ordered. But every commander should be made aware that in so using his men he is rendering some unfit for further duty, impairing others, and thus be led to count the cost of the frequent use of such active movements as carefully as he would the holding of a particular part of a line or the assault on another." To this excellent summary, a few personal impressions might be added by way of conclusion.

1. The *effort syndrome* is not a disease entity, but signifies a variety of symptoms resulting from different etiological factors, among which constitutional variation in individuals should be emphasized.

2. Prophylaxis is important to consider and among helpful procedures to this end a sufficiently prolonged period of convalescence is pre-eminent.

3. All recruits as well as convalescents from medical and surgical conditions should be subjected to competent functional tests before they are sent to front-line duty. Graduated exercises afford such a method of examination, and act, more-

over, as a therapeutic procedure, besides offering a good basis for the reclassification of soldiers.

4. Physicians in their constant thought of the pathological are often not thoroughly appreciative of the normal findings of, especially, the cardio-vascular and nervous systems.

5. The effort syndrome represents findings of varying and often slight changes from the normal which are by no means confined to soldiers, but are to be found constantly in the clinic of every physician.

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NOTES ON NEW BOOKS

Quarterly Medical Clinics. A Series of Consecutive Clinical Demonstrations and Lectures. By FRANK SMITHIES, M. D. Vol. I, No. I. Cloth $2.25, paper $1.50. (*St. Louis: Medicine and Surgery Publishing Company, 1919.*)

A large group of physicians throughout the country, especially those located away from the main centers, have always felt keenly the difficulty of keeping in touch with up-to-date methods in clinical medicine. To meet this demand, during the last few years a number of publications have sprung up, devoted to the teaching of medicine by the method of case histories and clinics. It is with interest, therefore, that we read the latest offering in this direction—the Medical Clinics of Dr. Frank Smithies.

In criticizing a work of this sort, one should have clearly in mind the purpose for which it is intended—to aid the student and the general practitioner. As the writer himself states in the preface, much of the material is elementary and treated along simple lines; but, at the same time, we find in these clinics well presented cases, with concise summaries of modern views as to etiology and treatment, together with sections on the technique of diagnostic and therapeutic procedures. Fifteen cases are taken up in the first volume, which deals mainly with abdominal diseases but also with other conditions. The general plan is well illustrated by Case 5, an instance of pernicious anemia. The history, examination and study of the case are first presented, followed by a section on differential diagnosis, and a discussion of severe chronic anemias in general, with particular reference to the changes in the hematopoietic system. Next comes a section on treatment, with a discussion of methods of transfusion and of testing the compatibility of the donor's blood. Finally, certain laboratory methods are given in detail.

The book is attractively gotten up, the material is arranged in convenient form and there are numerous excellent illustrations and diagrams. The value of the material would be considerably enhanced by the addition of a brief index. A. L. B.

Human Intestinal Protozoa in the Near East. By C. M. WENYON and F. W. O'CONNOR. (*London: John Bale, Sons and Danielsson, 1917.*)

This monograph of 210 pages represents a collection of four papers which appeared in the Journal of the Royal Army Medical Corps during the early months of 1917, to which has been added a fifth section made up of the clinical histories of patients studied and treated for intestinal protozoa. The authors have carried out an enormous amount of well-planned work, having studied almost 3000 cases, repeatedly examining many of the patients, and it is the result of this work that is reported. It is pleasing to note that their observations have confirmed almost all of the facts heretofore considered established in regard to protozoan infections of the intestine, and comforting to one with less experience that even these observers with such opportunities for studying the problem must still write, "It is often quite impossible to distinguish unencysted forms of E. histolytica from E. coli." Section IV detailing experiments with flies as carriers is most interesting, indeed startling, and may well be calculated to discourage casual travel in the regions in which this work was done. For instance, of two hundred flies caught at random in different localities in Alexandria, in the droppings of fifteen was found one or more of the following: cysts of E. histolytica, E. coli, Lamblia intestinalis, the oöcyst of a coccidium, and eggs of Taenia saginata, Ankylostoma duodenale, Trichuris trichuria, Heteroplyes, and Bilharzia. In another section therapeusis is discussed and the results obtained are enlightening but rather discouraging. Two intestinal flagellates and an amoeba are described which the authors believe have not been described before.

This monograph is a definite contribution to the subject of intestinal protozoa. The authors have used a splendid opportunity to good advantage. The subject matter is well presented, it makes interesting reading, and there is a good index. F. A. E.

The Soldier's Heart and the Effort Syndrome. By THOMAS LEWIS. Cloth $2.25. (*London and New York: Shaw and Sons, Paul B. Hoeber, 1918*).

Dr. Lewis has been the leader in the recognition and treatment of that recently acknowledged relative of all disease—Effort Syndrome. At Hampstead and later at Colchester, he taught his rational and practical views of the handling of heart disease, a medical condition that accounted for 10 per cent of all discharges from the British army. This experience and advice he sums up in clear, straight-forward language in the present book, "primarily written with the intention of helping medical officers of recruiting, discharging and pensioning boards, and medical officers in charge of patients." It has, however, more than a military application, for it discusses the methods of physical examination of the cardio-vascular system from a somewhat novel view-point. Many times I have heard Dr. Lewis bewail time lost in insignificant discussions of some of the manifold variations of the text-book pictures of health or disease! Test the patient's ability to perform exercise, functionally try him out! The army could not use a healthy heart in a man constitutionally inferior, whereas a slightly diseased heart in an otherwise healthy body was utilizable. We physicians are apt to overlook this practical problem in civilian life, and many a patient is consigned to a life of invalidism because of a heart condition that has been recognized as not normal. The reserve power of the vascular system is enormous, and even a badly affected heart can be intelligently managed so as to satisfy the demands of a controlled life. Perhaps the greatest lesson in Dr. Lewis's book is a new approach to the old story that many variations make up the normal. It is rarely possible to diagnose disease by one finding, and there is a general tendency to ascribe too much importance to the presence of sounds that are not encompassed in the regulation "lub-dupp" of the text-book. Careful physicians may not follow Dr. Lewis in his statement that accurate delineation of the heart's size by percussion is not possible, but his valuation of test exercise is not too high and is well worth the careful thought of all medical men. E. W. B.

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